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ALF SJÖVALL RESIGNS AS EDITOR 1 JULY 1970

Alf Sjövall in 1960 succeded Axel Westman as editor of this journal. In spite of all our attempts to persuade him to continue as editor he decided to resign at the same time as he leaves his chair of obstetrics and gynaecology in Lund. During his excellent editorship he not only devoted a large part of his time to editorial duties, which he performed admirably but he also put the journal on a sound economic basis. For me it is therefore a pleasant duty to thank him heartily on behalf of the editorial committee for all he has done to ensure the success of the journal. It was only in the hope of being able to call upon and benefit from Alf Sjövall's wide experience in years to come that I dared to accept the responsibility as the new editor

Axel Ingelman-Sundberg

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ISOLATED TORSION OF THE FALLOPIAN TUBE

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Abstract. After observing 2 cases of isolated torsion of the Fallopian tube, we inquired of all surgical and gynaecological departments on the Danish islands of Zealand and Lolland-Falster hether any such cases had been treated during the period 1957–1967. In this way we traced another 8 cases. As the departments concerned serve an area of Denmark ith population of about 3 millions, about half of hom are women, the annual incidence of isolated torsion of the Fallopian tube may be estimated as one in 1,500,000 women. The 10 case histories are briefly reported. Some theories on the aetiology of tubal torsion are mentioned, and the symptoms as well as treatment are discussed.

In 1962 Blair reported 4 cases of isolated torsion of the Fallopian tube. Reviewing the literature he found that since Bland-Sutton, in 1890, published the first known case, a total of about 300 had been reported. Since then another 30–40 cases have been added, e.g. by Walker (1962), Youssef et al. (1962), Koren & Zuckerman (1963), Frangipan (1964), Kendrich (1965), Abraham (1966), Christmas et al. (1966), and Granet et al. (1966). In this country only a few cases have been published, and none since 1929 (Krieger Lassen).

MATERIAL

W observed 2 cases of isolated torsion of the Fallopian tube in our department in short period. In order to elucidate the incidence of this condition in more detail, we sent inquiries to 53 surgical and gynaecological departments on the Danish islands of Zealand and Lolland-Falster asking hether such cases had been treated during the period 1957–1967. Replies were received from 50 departments here the diagnostic files had been perused. In this way another 8 cases were divulged, all of hich ill be reported below. Since the second 50 departments serve an area ith population of about 3 millions, half of hom are women, the annual incidence of isolated torsion of the Fallopian tube may be estimated to be one in 1,500,000 omen.

CASE REPORTS

Case 1. A 13-year-old nullipara who had been suffering from low abdominal pain for 2 ½ days. Owing to suspicion of appendicitis laparotomy was performed. This showed the distal half of the left Fallopian tube to be gangrenous and twisted 2 complete turns. The right tube was normal. The gangrenous part of the tube was removed, and plastic repair on the remaining part was done. Microscopic examination showed haematosalpinx with haemorrhagic infarction. Postoperative course uneventful.

Case 2. A 57-year-old oman who had been suffering, for about 6 months, from periodical left lower quadrant pain. On admission the pain had been increasing for 48 hours, and on vaginal examination soft, tender mass, the size of closed fist, was palpable on the left of the uterus. On suspicion of twisted ovarian cyst laparotomy was done, revealing the left tube gangrenous and twisted 5 turns. Micr. diagn.: Twisted sactosalpinx ith haemorrhagic infarct. Postoperative course uneventful.

Case 3. A 53-year-old nullipara with history of increasing, constant pain in the left iliac fossa for 3 days. As this was thought to be twisted ovarian cyst, laparotomy was performed, revealing the left tube banana-shaped, 15 cm long, gangrenous, and twisted 360°. Microscopic examination showed hydrosalpinx with haemorrhagic infarct. Postoperative course uneventful. Fifteen years previously the patient had undergone operation for similar condition, and at that time the right tube was found to be twisted 270°. The preoperative diagnosis was then appendicitis. At this former operation the left tube had been entirely normal.

Case 4. A 29-year-old oman with a 3-day history of increasing bouts of pain in the right iliac fossa. Six years previously she had been admitted for bilateral chronic salpingitis. Owing to suspicion of twisted ovarian cyst laparotomy was done. The right tube, which was gangrenous, was found to be twisted 2 complete turns. On the left she had hydrosalpinx measuring 5 4 3 cm. Postoperative course uneventful.

Case 5. A 47-year-old woman was admitted for acute appendicitis after having had increasing pain in the right iliac fossa for 2 days. Menopause 18 months previously. On vaginal examination an oblong, tender mass was palpable on the right of the uterus. This was believed

to abnormal motion of the internal genitalia. This may be the explanation of our case 7. The traumatic theory, i.e. that accidents and other traumas may lead to torsion, is in keeping with Sellheim's theory. That earlier operation on the internal genitalia may lead to torsion has been demonstrated by Kohl (1956) and Kendrich (1965), each of whom reported a case of torsion arising in women with a history of sterilization by the Pomeroy method. Blair (1962) mentioned the so-called physiological theory that disturbances of the normal peristaltic movements of the tube, possibly in the form of spasms, may lead to torsion. He hinted that certain drugs might perhaps cause such spasms. Apart from these possible causes, purely anatomical changes must be able to cause tubal torsion. Such changes may be among others, a long, narrow mesosalpinx, a paraovarian cyst, or persistence of the spiral winding which is normally seen in the foetal tube. Although no patient of the present series was pregnant, it may be mentioned that the phenomenon is not uncommonly associated with the latter half of pregnancy. Out of Regad' (1932) patients 12 ... were pregnant, and cases in pregnant patients have been published by Grasset et al. (1966), Chastrusse et al. (1966), and Walker (1962). In 3 out of 6 cases of tubal torsion Yoursef et al. (1962) found an enlarged uterus. Two of the patients were pregnant, while the third had large fibromyomas. In all the present patients the uterus was of normal size.

In the course of time many authors have discussed whether torsion can occur in the normal tube. Yoursef et al. (1962) believed not only that this was possible, but that in most cases of torsion the tube was normal. Blair (1962) was more sceptical, stating that it had never been proved that the tube had been normal before torsion occurred. Seven of our patients had hydro- or haematosalpinx. Of course, we are unable to tell whether these changes were caused by or had caused the torsion. Apart from a gangrenous tube of the patients (cases 7 and 9) showed no abnormality of the tube or neighbouring organs. This would seem to indicate that in fact a normal tube may get twisted. The observation that isolated torsion of the tube, unlike e.g. torsion of ovarian cysts, apparently never occurs in elderly women may perhaps be due to the postmenopausal atrophy of the tube and its vascular supply.

The symptoms of tubal torsion are primarily constant pain and tenderness in the lower part of the abdomen on the affected side. In the presence of hydro- or haematosalpinx vaginal examination usually reveals a palpable mass. In a few cases there may be nausea and vomiting as well as slight vaginal bleeding. In spite of the very severe pain the patients are seldom in shock. Seven of our cases had a marked elevation of the ESR, and in half the cases the temperature was elevated, up to 38.5°C. The diagnosis does not appear to have been made preoperatively in any of the previously published cases. This is due to the rarity of the condition and to the difficulty in differentiating it from acute appendicitis, torsion of an ovarian cyst, extrauterine pregnancy and commonplace salpingitis. The lesion is more common on the right. In the present series there were 6 right-sided, 3 left-sided, and 1 bilateral case.

The treatment of tubal torsion must invariably be surgical. In most cases salpingectomy is necessary, but if gangrene has not yet appeared, it may occasionally be enough to untwist the tube. Blair (1962) and Yoursef et al. (1962) have reported successful treatment by this means. In one of our cases (case 1) only the extreme end of the tube was gangrenous. This part was excised, and plastic repair of the remaining part was done. This treatment appears to be ideal, as the patients are nearly always children or women of the fertile age.

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The author acknowledges his indebtedness to Professor H. Faber, M.D., and to Drs T. Cl. Gertz, M.D., P. A. Gierup, M.D., H. Engberg, M.D., R. Hammen, M.D., and E. Henochsen, M.D., for the permission to publish the cases from their departments.

REFERENCES

Abraham, A. J. Indian Med Ass 47 797. 1966.
Blair, C. R. Surg Gynec & Obstet 114 727. 1962.
Chastrusse, L., Sennecq, M., Sommerow-Mouret, J., Malevale, G. & Pailler, J. C. Bull Fed Gynec Obstet Franc 18 259. 1966.
Frangenon, G. Am Obstet Gynec 86 514. 1964.
Grasset, J., Klein, M. & Ngohon-Bonerat. Bull Fed Gynec Obstet Franc 18 18. 1966.
Kendrich, J. G. Obstet Gynec 25 124. 1965.
Kohl, G. C. Obstet Gynec 7 396. 1956.
Karen, Z. & Zuckerman, H. Gynaecologica 155 387. 1963.
Lasen, H. Kruger: Hospitalstidende 72 947. 1929.

Table 1 *Ten cases of isolated torsion of the Fallopian tube*

Case	Age (yrs)	History of salpingitis	Side affected	Max. temp. (°C)	Max. ESR	Duration of illness	Degree of torsion
1	13	No	Left	38.4	43	½ days	360°
	37	No	Left	37	76	Ab 6 mo.	360° 5
3	53	No	Bilat.	38	3[illegible]	3 days	360 and 720
4	79	Yes	Right	37.[illegible]	8	3 day	360°
5	47	No	Right	38.2	10	days	360° 3
6	41	Yes	Left	37	38	1 day	360
7	19	No	Right	37.3	5	1 mo	360°
8	44	Yes	Right	38.5	43	days	360 3
9	47	Yes	Right	37.3	63	1 day	
10	36	Yes	Right	37 6	4	1 day	360 4

to be a twisted ovarian cyst, and operation was per formed. The right tube, which was twisted 3 turns, was dilated and gangrenous. Microscopic examination revealed a tube with haemorrhagic infarct. Postoperative course uneventful.

Case 6 A 41-year-old nullipara who had been having severe constant pain over the left inguinal ligament for 4 hours. History of syphilis 20 years previously Operation revealed the left tube twisted 360° almost gangrenous, and converted into a blood-filled coach horn Right tube thickened and oedematous. Microscopic examination revealed acute non-specific inflammation and incipient necrosis of the tubal wall. Postoperative course uneventful.

Case 7 A 19-year-old nullipara with history of fairly mild, constant pain in the right iliac fossa for about one month. Allegedly the pain had started after heavy lifting. During the past 48 hours the pain had increased considerably and laparotomy was done on the suspicion of a twisted ovarian cyst. The distal half of the right tube was found to be twisted complete turns. The affected part was entirely gangrenous. Post perative course uneventful.

Case 8 A 44-year-old woman with increasing dull pain in the right iliac fossa for 48 hours. 18 years previously the patient had been admitted for bilateral salpingitis. Laparotomy showed on the right a gangrenous, twisted hydrosalpinx filled with haemorrhagic fluid. Salpingectomy was performed, and the postoperati course was uneventful.

Case 9 A 47 year-old woman with increasing pain in the right iliac fossa for 4 hours. 1 ars previously she had been admitted with pelvic inflammation. Menopause 6 months before the present dmission Laparotomy was done on a suspicion of ppendicitis but it revealed the right tube to be twisted and gangrenous Microscopic examination: A tube with haemorrhagic infarct. Post operative course uneventful

Case 10 A 36-year-old woman who had been having severe pain across the lower abdomen for the past 1 hours Four months previously the p tient had been treated with penicillin for pel ic inflammation, and 4 days before admission she had brief episode of dull pain in the right iliac fossa. Owing t suspicion of twisted ovarian cyst exploratory laparotomy was done This revealed parao arian cyst, as large as a goose's egg, and a tube 15 cm long and twisted 4 turns in the middle. Microscopic examination: Fallopian tube ith marked haemorrhagic infarction. Fibrinopurulent perisalpingitis.

DISCUSSION

This study has shown that isolated torsion of the Fallopian tube is rather more common than the literature leads one to believe

It occurs most often during the menstruating years. Among 201 cases Regad (193?) found that [illegible]0 occurred before puberty while the remaining 80% affected women in the age range 13–49 years. Cases among postmenopausal women do not appear to be on record. In the present material the youngest patient was 13 years, while the oldest one was 53—average 36 years. In three of our cases (cases 3 5 and 9) the menopause had occurred from 6–18 months previously One of these patients (case 3) had undergone operation for torsion of the contralateral tube 15 years ago Such cases of bilateral tubal torsion are extremely rare Youssef et al (196[illegible]) claimed that including their own case 13 were on record, but to these may be added the case of bilateral torsion in a 16-year-old girl reported by Rogers in 19[illegible]5

Several theories have been advanced concerning the aetiology of tubal torsion In experimental studies Payr (1906) found a tendency to torsion in organs where venou congestion arises Since the veins of the mesosalpinx are longer and more flexible than the arteries, they ought to be able to cause torsion of the tube in the event of enous congestion Sellheim's (19[illegible]) theory is that ud den changes in the position of the body may lead

to abnormal motion of the internal genitalia. This may be the explanation of our case 7. The traumatic theory, i.e. that accidents and other traumas may lead to torsion, is in keeping with Sellheim's theory. That earlier operation on the internal genitalia may lead to torsion has been demonstrated by Kohl (1956) and Kendrich (1965) each of whom reported case of torsion arising in women with a history of sterilization by the Pomeroy method. Blair (196_) mentioned the so-called physiological theory that disturbances of the normal peristaltic movements of the tube, possibly in the form of spasms, may lead to torsion. He hinted that certain drugs might perhaps cause such spasms. Apart from these possible causes, purely anatomical changes must be able to cause tubal torsion. Such changes may be among others, long, narrow mesosalpinx, a paraovarian cyst, or persistence of the spiral winding which is normally seen in the foetal tube. Although no patient of the present series was pregnant, it may be mentioned that the phenomenon is not uncommonly associated with the latter half of pregnancy. Out of Regad' (193) patients 1 % were pregnant, and cases in pregnant patients have been published by Grasset et al. (1966), Chastrusse et al (1966), and Walker (1962). In 3 out of 6 cases of tubal torsion Youssef et al (1962) found an enlarged uterus. Two f the patients were pregnant, while the third had large fibromyomas. In all the present patients the uterus was of normal size.

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REFERENCES

Abraham, A. J. Indian Med Ass 47 297 1966.
Blair C. R. Surg Gynec & Obstet 114 777 1962.
Chastrusse, L., Sentucq, M. Sommeron-Mourat, J. Malemin, G. & Pailler J. C. Bull Fed Gynec Obstet Franc 18 259 1966
Frangipan, G. Ann Obstet Gynec 86 514 1964
Grasset, J. Klein, M. & Mpobon-Bonevat: Bull Fed Gynec Obstet Franc 18 18, 1966
Kendrich, J. G. Obstet Gynec 25 1 4, 1965
Kohl, G. C. Obstet Gynec 7 396, 1956
Koren, Z. & Zuckerman, H. Gynaecologica 155 387 1963.
Lauren, H. Kruger Hospitalstidende 72 857 1929

Regad, J La Torsion des Trompes Utérines. Librairie Cannugli, Lyon, 1932.
Rogers, L. Brit Med J *1* 778, 19_5
Walker P A. J Obstet Gynec Brit Comm 69 117 196_
Youssef, A. F Fayad, M. M & Shafeek, M A. Acta Obstet Gynec Scand *41* 29_, 196_

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CYTOLOGIC FINDINGS AND THEIR SIGNIFICANCE IN GYNAECOLOGY

Clinico-Pathologic and Cytologic Correlation

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Abstract Detection of tumour cells in cervicovaginal secretions nearly always indicates the presence of malignant tumour or epithelial dysplasia. Presence of suspicious cells or cells with atypical nuclei very often suggests the existence of malignant tumour or epithelial dysplasia (46 and 14% respectively). The great majority of the remaining patients with such cytological changes suffer from other gynaecological diseases, most often of an inflammatory nature. A cytologic differentiation between these groups is not yet possible. Other examinations are therefore indicated. Cytological changes in the cervicovaginal secretion rise in frequency with increasing age. In 9% of the patients with carcinoma of the cervix no abnormal cells were detected in the cervicovaginal secretions. The corresponding figures for severe ("carcinoma in situ") and moderately severe epithelial atypia were 22 and 31% respectively. No more than one third of the patients with carcinoma of the uterine body had abnormal cytology. Hence, on the slightest suspicion of malignancy we should not rely on "negative cytology" and especially not as the result of single examination.

Carcinomas of the uterine body generally manifest themselves by bleeding disorders. The diagnosis is to be established on the basis of curettage.

In the present series the cytologic examination decided the diagnosis and treatment in no more than single case of cervical carcinoma. Cytologic examination therefore seems to be of limited value for patients admitted to gynaecological ward, where other diagnostic aids are available. On the other hand, the method is believed to be of value in practice, when we bear in mind that, like other methods, it is vitiated by certain margin of error. On the slightest clinical suspicion of malignant or premalignant disease we should not rest content with single negative examination.

The correlation between cytologic and biopsy findings in a series of 775 female patients was discussed in a previous paper (Sjølin & Hornbæk, 1964).

For the present study this series was amplified so as to comprise a total of 2055 women.

METHOD

Smears were examined from the cervical orifice, except where total hysterectomy had been done, and from the posterior fornix. The first one-third of the specimens were fixed immediately with 95% ethanol, and the remainder with "Pro-Fixx".

The medical staff of the department subjected all the preparations to microscopic study. At that point of time nothing was known about possible changes in simultaneously taken biopsy specimens, where such were available.

As in the previous investigation, distinction was made between tumour cells, cells suspicious of malignancy and cells with atypical nuclei. The latter are cells with enlarged, but regular nuclei. Cases with atypical epithelium or dysplasia were classified according to Christensen (1962): mild epithelial atypia, moderately severe epithelial atypia, and severe epithelial atypia or carcinoma in situ (see also Lyng & Henriksen, 1968).

MATERIAL

This report includes, as stated, examinations of specimens from 2055 consecutive female patients treated in the Department of Gynaecology Sønderbro Hospital, between May 1, 1963 and the end of March 1964. In the cases where the same patient was subjected to two or more cytologic examinations the most severe cytological change was used as the basis for the patient's allocation to one of the stated groups.

Table I illustrates the age distribution of the series. Half of the patients belonged to the age group of 35–54 years.

It is seen in Table II that tissue specimens for histological examination were available from barely two-thirds of the patients. These comprised biopsy specimens from the vaginal portion, endometrium, cervical mucosa, and other surgical preparations.

Table I *Age distribution of 2055 patients*

Age in years	15–24	25–34	35–44	45–54	55–64	>64
No of patients	334	375	502	560	172	112

Table II *Histologic examinations*

	+ Biopsy of vag. port.	+ Curettage no biopsy of vaginal portion	Other surg. preps. no vag. port. biopsy no curettage	No ti ue
No. of patients	1164	1?0	99	67?

Table III *Results of cytologic examinations*

+ Tumour cells	− Suspicious cells	Nuclear atypia	No abnormality
19	89	189	1758

Table IV *Age distribution of patients with abnormal cell findings*

Age in years	15–24	25–34	35–44	45–54	55–64	>64
Tumour cell	0	2	6	6	4	1
Suspicious cells	3	13	23	31	8	11
Nuclear atypia	22	25	3	64	25	1

Abnormal cytology was demonstrated in 297 (just over 14 %) of the 2055 patients. The classification of the cytological changes is shown in Table III.

The age distribution of the patients with abnormal cell findings is illustrated in Table IV. In patients below the age of 25 no tumour cells were found, but both cells with atypical nuclei and cells suspicious of malignancy were found.

19 patients showed tumour cells in their smears. One of these had an erosion of the cervix without epithelial dysplasia (Table V) and this specimen must be classified as false positive. Re-evaluation of this case did not result in re-classification of the abnormal cells.

The histological diagnoses of 89 patients with suspicious cells in the cervicovaginal secretion have been set out in Table VI. Of these, 13 had cancer of cervix, 1 cancer of the body and 1 vulval carcinoma. Further 1 had vaginal metastases from previously treated cancer of the body and 1 a vesicovaginal fistula resulting from vesical carcinoma. 4 patients had different degrees of atypical epithelium of the vaginal portion, ranging from the severest degrees ("carcinoma in situ"), in 5 cases, to the mild, in 10. 48 had no signs of malignant or premalignant disease, but the majority suffered from gynaecological diseases, most often of an inflammatory nature and had benign tumours (Table VIa). No further data are available on the remaining 10 patients, of whom some failed to appear for follow-up examination.

Secretions from 189 patients (Table VII) had cells with atypical nuclei. Of these, 4 had cancer of the cervix, 3 cancer of the body. 20 showed different degrees of atypical epithelium (or dysplasia), and of these had severe epithelial dysplasia. 149 patients showed no malignant or premalignant epithelial changes. The majority of these had inflammatory gynaecological diseases (Table VII). In 13 cases no further details could be obtained.

Table VIII shows the age distribution of the patients with abnormal cell findings and all degrees of epithelial dysplasia (from mild dysplasia to carcinoma). The per

Table V

+ *Tumour cells*
Carcinoma of the cervix
Severe epithelial atypia of the cervix
Mild epithelial atypia of the cervix
Erosion of the cervix

Table VI

+ *Suspicious cells*
Carcinoma of the cervix
Severe epithelial atypia of the cervix
Mod. severe epith. atypia of the cervix
Mild epithelial atypia of the cervix
Adenocarc. of the uterine body
Planocellular vulval carcinoma
Metastasis to the vagina
Vesicovag. fistula from bladder carcinoma
No epithelial atypia

Table VI*a*

Suspicious cells without epithelial atypia
Cervicitis erosion
Genital prolapse
Urethral caruncle
Salpingitis
Parametritis
Bilat. serous cystadenoma
No histologic or clinical data

Table VII

− *Nuclear atypia*	
Carcinoma of the uterine cervix	
Severe epithelial atypia (vag. portion)	
Mod. severe epithelial atypia (vag. portion)	
Mild epithelial atypia (vag. portion)	
Adenocarcinoma of the uterine body	
No epithelial atypia	1

...centage with abnormal cells rose steadily in the older age-groups. The age of occurrence of epithelial abnormalities (dysplasia to carcinoma) is recorded in the same table. It is seen that from the age of 25 the incidence of dysplasia–carcinoma remained at about 6–8% as compared with 2% in the youngest age group. The age distribution for cases of epithelial dysplasia and carcinoma is detailed in Table VIII a. No patient below the age of 25 had carcinoma, but two had moderately severe epithelial dysplasia.

Table IX illustrates the relation between the carcinomas and atypical epithelium on one hand and the cytologic

Table VII

Atypical cell nuclei, without atypical epithelium	*162*
Cervicitis/erosion	98
Vaginitis	10
Trichomoniasis	2
Genital prolapse	8
Salpingitis	2
Salpingo-oophoritis	3
Parametritis	6
Ovarian cyst	1
Bartholinitis	2
Urethral caruncle	1
Pregnancy	3
Menostasis	1
Menorrhagia	1
Metrorrhagia	3
Retroflexion of the uterus	1
Condylomata	1
Fibromyoma	1
Prolapse of vertebral disc	1
Observation (anaemia)	2
Carcinoma of the breast	1
Fibroma of the skin	1
No histologic or clinical data	13

Table VIII. *Age distribution of all abnormal cell findings, and of all patients with dysplasia and carcinoma of the female genitals*

Age in years	15–24	25–34	35–44	45–54	55–64	> 64
Abnormal cell	25	40	61	101	37	33
findings	7	11	12	18	22	29
Dysplasia	8	21	40	35	14	8
carcinoma	2	6 %	8	6	8	7

Table VIII

Age in years	15–24	25–34	35–44	45–54	55–64	64
Carc. of vag. portion	0	4	15	7	5	1
Carc. in situ	0	4	6	8	0	0
Mod. severe epith. atypia	2	7	5	5	0	0
Mild epithelial atypia	6	6	11	13	3	2
Carc. of uterine body	0	0	2	2	4	4
Ovarian carc.	0	0	1	0	2	1

Table IX

Hist. diagnosis	Carc. of vag. portion	Carc. in situ	Mod. severe epith. atyp.	Mild epith. atypia	Carc. of uterine body	Ovarian, etc.
Total tumour cells	12	4	0	2	0	0
Total suspicious cells	13	5	9	10	1	0
Nuclear atypia	4	3	4	11	3	0
Cytology negative	3	4	6	18	8	4
Total	32	18	19	41	12	4

findings on the other. Three out of 32 carcinomas of the vaginal portion (just over 9%) showed no cytological changes. However, in 4 out of 18 cases of severe dysplasia (22%) no abnormal cells were detected. The same was true in 6 out of 19 cases of moderately severe dysplasia (31%), and in 18 out of 41 cases of mild epithelial dysplasia (44%). Eight out of 12 carcinomas of the body (67%) were cytologically negative.

Whether tumour cells in the secretion always can be demonstrated on the first examination, or whether a greater number of examinations is required, is a question which warrants elucidation.

Table X gives the numbers of examinations made in the 19 cases with tumour cells. In 14 of these, the first examination disclosed tumour cells. In 3 tumour cells were not detected till the second examination, but in one of these, abnormal—suspicious—cells had been found at the first examination. In 2 patients tumour cells were first demonstrated at the third examination. In these cases the first and second examinations showed atypical nuclei and suspicious cells.

A corresponding tabulation has been made for the 89 patients whose secretions contained suspicious cells (Table XI). In 71 of them the first examination and in 12 the second examination revealed suspicious cells. However, in 7 of the latter 12, abnormal cells (atypical nuclei) were noticed at the first examination. Five patients did not present suspicious cells till the third examination and one not till the fourth.

Eight of the 18 patients of this group showed atypical nuclei on the first examination.

The following histological diagnoses were recorded for the 12 patients who displayed suspicious cells on the second examination:

4 cervical tears with nonspecific inflammation
1 subacute salpingitis
1 metastasis to the vagina from previously removed adenocarcinoma of the uterine body
1 vulva carcinoma
1 carcinoma of the cervix
1 severe dysplasia (carcinoma in situ)
1 moderately severe epithelial dysplasia
2 no tissue

The four patients in whom suspicious cells were not detected till the third examination subsequently had the following histological diagnoses made:

Table X

No of cyt. examinations of each patient	Total tumour cells on examination no		
	I	II	III
1	5		
2	6	1 –1[a]	
3	3		1[b]
4			1
5		1[d]	
	14	3	2

Histological diagnosis planocellular carcinoma of the uterine portion.

[b] Examinations I and II showed, respectively nuclear atypia and cells suspicious of malignancy Histological diagnosis. mild epithelial atypia.

Examinations I and II showed, respectively nuclear atypia and suspicious cells. Histological diagnosis planocellular carcinoma of the uterine portion.

[d] Examination I showed suspicious cells. Histological diagnosis. tissue from vaginal portion with severe epithelial atypia (or carcinoma in situ").

Histological diagnosis planocellular carcinoma of the uterine portion.

– moderately severe epithelial dysplasia

– mild epithelial dysplasia

The last patient, in whom suspicious cells were found on the fourth examination, had previously been operated on for bilateral ovarian serous cystoma. The abnormal cytological picture subsequently subsided.

DISCUSSION

Cytological terminology

In the present material the abnormal cells were classified in three groups. tumour cells, cells suspicious of malignancy and cells with atypical nuclei. This classification is employed by most pathologists in this country It has the advantage of being used also in other fields of exfoliative cytology A few clinicians have expressed a desire to have the cytology classified merely as positive when abnormal cells are demonstrated and negative in the remaining cases. This desire is understandable in so far as even the slightest cellular abnormality nuclear atypia may indicate the presence of cancer On the other hand, there is reason to point out that just over four fifths (84) of the patients with tumour cells had manifest carcinoma or "carcinoma in situ" (Table V) The corresponding percentage for patients with suspicious cells was 42 (incl metastases and vesical carcinoma) and that for all patients with atypical nuclei was 6. Thus even though the slightest cytological changes may suggest the presence of cancer the chance of this is considerably smaller than when tumour cells are found. Nevertheless such changes indicate the need for careful examination of the patient.

For didactic reasons it is also important that the examiner is compelled to judge the qualitative changes.

If we compare the terminology used in the present paper with that employed by Papanicolaou & Traut (1943) tumour cells correspond to class 5 suspicious cells to classes 3 and 4 atypical nuclei to class 2, and no abnormality to class 1

Correlation between cytology and histology

Positive cytology

It has been stated previously that the severest cytological changes most often are accompanied by the severest tissue changes.

Among the 19 patients reputed to have tumour cells present (Table V) there was one false positive diagnosis. Nevertheless, after re-evaluation the cytological findings were still regarded as tumour cells. A subsequent examination revealed no tumour cells. The erosion had then healed.

The remaining 18 patients presented epithelial dysplasia of different degrees, ranging from the mildest forms to carcinoma. Note, however that even the mildest degrees of epithelial dysplasia (2) may cause desquamation of cells having the appearance of tumour cells.

Within the tumour cell group one patient had the diagnosis of cancer established on a cytological basis. The cytological diagnosis together with the clinical symptoms of pain and menstrual disorders indicated the need for operation. Repeated biopsies and curettage did not disclose the presence of cancer in this patient, but an intracervical carcinoma was demonstrated in the surgical specimen. Shortly after the collection of the present material had been concluded we had another patient of the same type

Carcinomas and epithelial dysplasia were found in barely half of the group of patients with cells suspicious of malignancy This group includes, as stated, a patient treated previously for adenocarcinoma of the uterine body Metastasis to the vaginal wall was noticed at the time of the present investigation. Another patient had a vesical carcinoma with a fistula into the vagina.

In the group with atypical cell nuclei there were 7 patients with carcinoma and 20 with epithelial dysplasia. Thus, the slightest cytological changes may indicate the presence of carcinoma, which therefore must be excluded before the patients can be declared fit.

False positive

The remaining 162 patients (Table VII *a*) with *nuclear atypia together with the 48 having suspicious* cells without epithelial dysplasia (Table VI *a*) and the patient with erosion and tumour cells, may in fact be classified as "false positive. However there is reason to point out that they all, except about 10% for whom further data were not available, suffered from a great variety of gynaecological diseases, chiefly of an inflammatory nature. The abnormal cells must be supposed to represent reactive phenomenon against these diseases, presumably hyperplasia.

Accordingly the conclusion may be drawn that the presence of abnormal cells in cervicovaginal secretions nearly always indicates the presence of gynaecological disease, whether of a neoplastic or other nature. We cannot yet in all cases distinguish cytologically between these groups of diseases, but must resort to other methods of gynaecologic examination.

Age

As stated above, tumour cells were not observed in patients under 25 years of age, whereas both suspicious cells and cells with atypical nuclei were seen in this age group. In the present series neither carcinoma nor severe epithelial dysplasia was demonstrated in this group, but cases with mild and moderately severe epithelial atypia were observed (Table VIII *a*). The latter condition is treated by conisation, which often gives surprising information (Lyng & Henriksen, 1968). Severe epithelial dysplasia and carcinoma of the uterine portion were recorded among patients from the age of 25. These diseases occur in the fairly young age classes (Clemmesen, 1964).

False negative

Unfortunately there may be found a so-called false negative cytology, i.e. absence of abnormal cells, even after re-evaluation, in secretion from patients with malignant tumours (Table IX). In the present series this was so for 9% of the

Table XI

No. of cyt. examinations of each patient	Total suspicious cells on examination no.			
	I	II	III	IV
1	36			
2	16	6[a]		
3	8	1	2	
4	6	2	1	
5	3	1	1	
6		1	1	1
7	1			
8		1[a]		
9				
10	1			
	71	12	5	1

One showed nuclear atypia.

carcinomas of the vaginal portion. Strangely enough, this figure is identical with that arrived at in a previous study (Sjölin & Hornbæk, 1964) and almost identical with that calculated by Bredahl & Lefèvre (1965): 11%. Cytology may thus fail in about 10% of the patients with carcinoma of the vaginal portion. The corresponding figures for severe and moderately severe dysplasia are 22 and 31% respectively.

This is disappointing in a way, but, on the other hand, we must bear in mind that even if a vaginal portion biopsy reveals no signs of carcinoma, this does not preclude presence of a carcinoma in this portion (Lyng & Henriksen, 1968).

Abnormal cells were found in no more than one-third of the patients with carcinoma of the uterine body. Bredahl & Lefèvre (1965) noticed abnormal cells in just over half of such patients. In other words cytology cannot be relied upon to establish the diagnosis, when carcinoma of the uterine body is suspected. A curettage is required for making this diagnosis.

Repeated examinations

Tables X and XI illustrate that abnormal cells do not always manifest themselves on the first cytologic examination. Thus, no tumour cells or suspicious cells were detected in the first specimen of secretion from eight patients with carcinoma (vaginal portion, vulva, vagina) although they were disclosed in the second or third examination. However the first examination disclosed suspicious cells or nuclear atypia in all the patients of the tumour

cell group Hence on the slightest suspicion of malignancy we should not rest content with a "negative cytology" on a single examination.

REFERENCES

Bredahl, E. & Lefèvre H Act Obstet Gynec Scand 44 Suppl. 2, 348 1965
Clemmesen, J Ugeskr Læg 1 4 879 1962.
Clemmesen, J Statistical studies in malignant neoplasma I, pp 330-332, Munksgaard, København, 1965
L ng, J & Henriksen, B Ugeskr Læg 130 1120 1968
Papanicolaou, G N & Traut, H. F Diagnosis of uterine cancer by vaginal smear N Y 1943
Sjolin, K. E. & Hornbak, H. Ugeskr Læg 1 6 546, 1964

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NUCLEAR INCLUSION BODIES IN VAGINAL SMEARS FROM PATIENTS WITH VAGINAL DISCHARGE

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Abstract. One hundred women with acute vaginal discharge were examined clinically, cytologically and virologically for herpes simplex. Eleven of them showed cytological signs of herpes simplex, a diagnosis that was confirmed virologically in 5. This frequency of cytological and virological changes is much higher than that found in routine smears. Gynaecological examination showed signs of herpes genitalis in only 3 cases.

A specific type of inclusion body in vaginal smears, previously reported by various workers (Varga & Browell, 1960; Stern & Longo, 1963; Yen, Reagan & Rosenthal, 1965; Naib, Nahmias & Josey, 1966), has also been found in routine smears submitted for cancer detection at Malmö General Hospital. In 1967 Naib produced evidence suggesting that these inclusion bodies are produced by herpes simplex virus. In a previous study (Cederqvist, Eliasson, Lindell & Stormby, 1968), which lent support to the theory that this type of inclusion body is brought about by the above mentioned virus, it was noticed that these bodies were demonstrated mainly in women who had vaginal discharge at the time of the examination. Since patients with this condition are usually not examined cytologically until the infection has healed, by which time herpes viruses, if any, may no longer be demonstrable, it was decided to undertake a clinical, cytological and bacteriological-virological investigation of patients with acute vaginal discharge, as soon as they sought medical advice.

MATERIAL AND METHODS

The material consisted of 100 women selected at random among those who sought advice at the department of gynaecology because of vaginal discharge. Vaginal and cervical smears were obtained and stained by the Papanicolaou method. In the search for herpes simplex the criteria recommended by Naib, Nahmias & Josey (1966) were used, i.e. demonstration not only of nuclear inclusions (Fig. 1) but also of the characteristic nuclear moulding of multinucleated cells (Fig. 2).

Attempts were made to isolate the virus from all of the 100 patients. In 6 of the patients samples were collected on 2 occasions. The following types of cells were used: MASA cells from sternal bone marrow puncture of a male patient with infective hepatitis (Kjellén, 1961) and BS-C-1 monkey kidney cells. In 41 cases attempts were made to isolate virus also by culture on embryonic human skin-muscle cells. Each specimen was inoculated into 2–4 tubes of each type of tissue culture. The BS-C-1 and the skin-muscle tissue cultures were examined for 2 weeks. The inoculated MASA-cell cultures were passaged once after one week and examined for another week. All but one of the samples were examined also on the dropped chorio-allantoic membrane of embryonated eggs. Egg cultures were passaged once.

Cultures showing a cytopathogenic effect were transferred to new tissue cultures in tubes and to eggs. Suspected pocks on the egg membranes were transferred to new eggs and to tissue cultures. The haemagglutination test was performed on positive egg membranes with hen's erythrocytes at 37°C.

The interval between collection of the sample and its arrival at the laboratory was at most 2 hours, except for a few specimens collected during the night, which were stored at +4°C until they were sent to the laboratory. All samples were inoculated either immediately on arrival at the laboratory or after storage at −70°C. The cytological and virological studies were done independently. The results were not correlated until each study was terminated. Material was obtained at the same time from the urethra and cervix and cultured for gonococci. At the investigation, which included careful gynaecological examination, the women were also asked whether they or their sex partners had ever had manifestations of herpes simplex.

cell group. Hence, on the slightest suspicion of malignancy we should not rest content with a "negative cytology" on a single examination.

REFERENCES

Bredahl, E. & Lefèvre, H.: Acta Obstet Gynec Scand 44 Suppl. 2, 348, 1965.
Clemmesen, J.: Ugeskr Læg 124: 879, 1962.
Clemmesen, J.: Statistical studies in malignant neoplasms I, pp. 330-332. Munksgaard, København, 1965.
Lyng, J. & Henriksen, B.: Ugeskr Læg 130: 1120, 1968.
Papanicolaou, G. N. & Traut, H. F.: Diagnosis of uterine cancer by vaginal smear. N.Y. 1943.
Sjølin, K. E. & Hornbak, H.: Ugeskr Læg 126: 546, 1964.

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or cytological manifestations. Four patients were pregnant. Two of them were cytologically positive and both aborted spontaneously in the third and fourth month of pregnancy. In one of these the diagnosis was verified virologically.

I 20 patients (20%) the anamnesis suggested that they had previously had herpes labialis or genitalis. Four of them belonged to the 11 patients of the cytologically positive group. Only one woman reported herpes like manifestations in her sexpartner. She was clinically suspected to have herpes genitalis, which was verified both cytologically and virologically.

DISCUSSION

Cytological changes suggesting herpes simplex are not often seen in routine vaginal smears submitted for cancer detection. Naib, Nahmias & Josey (1966) found such changes in smears from 62 (0.16%) of 40,000 patients. Such smears often show signs of general infection. Varga & Browell (1960) reported 11 cases with the same type of cytological changes of herpes. The general infection was severe in 9 and moderate in 2. Of the 100 women with clinically copious vaginal discharge in the present investigation, 11% proved cytologically positive for herpes simplex, which is much higher than expected in an unselected series of vaginal smears. The frequency at our laboratory in 1968 was 0.04% (68,000 patients).

Slavin & Gavett (1946) were first to isolate herpes virus from a woman with acute vulvo-vaginitis and in 1965 Nigogosyan & Mills diagnosed herpes ulcers of the cervix. Cytological changes suggesting viral infection have been noted by several observers during the screening of routine vaginal smears (Varga & Browell, 1960; Stern & Longo 1963; Yen, Reagan & Rosenthal, 1965; Naib, Nahmias & Josey 1966; Nahmias, Naib, Josey & Clepper 1967; Cederqvist, Eliasson, Lindell & Stormby 1968). In such series the herpes simplex diagnosis has been virologically confirmed in up to 43% on return visit after the initial cytological observation, which is of great interest because this virus is rare in routine gynaecological material (Christian, Ladevici, Miller & Riley 1965; Nahmias, Naib, Josey & Clepper 1967). Since the cytological changes are transient it was thought that the virus could probably be isolated much more often if material for culture were collected at the same time as the vaginal smears. This was done in the present investigation and we isolated herpes simplex virus in 45% of the cytologically positive cases, compared with 17% in our previous investigation where the patients had to return for virological confirmation of the initial cytological diagnosis.

Possible venereal transmission of the infection has been reported (Sharlit, 1940; Slavin & Gavett, 1946). Gonococci and Trichomonas were found twice as often in the cytologically positive group as in the entire series, which supports this possibility. No evidence is available of any relationship between infection with gonococci or Trichomonas and the cytological changes found. It should be observed that herpes simplex can run a course producing no clinical manifestations except vaginal discharge, which makes the diagnosis difficult.

Two pregnant women with herpes simplex aborted spontaneously some time after the examination, while 2 others without this infection went on to term. This is noteworthy because herpes simplex virus in the cervix can reach the foetus by transplacental transmission (Mitchell & McCall, 1963) and in tissue cultures it causes a high percentage of chromosome aberrations (Stich, Hsu & Rapp, 1964). Herpes simplex has been suggested as a possible cause of congenital malformations (Cederqvist, Eliasson & Lindell, 1967). The present investigation suggested that herpes simplex might also be a cause of spontaneous abortion.

REFERENCES

Cederqvist, L., Eliasson, G. & Lindell, L. Brit Med J 3 558, 1967.

Cederqvist, L., Eliasson, G. Lindell, L. & Stormby, K. Acta Cytol 1 413, 1968.

Christian, R. T. Ladevici, P. P. Miller, N. F. & Riley, G. M. Amer J Obstet Gynec 91 430, 1965.

Karblén, L. Virology 14 234, 1961.

Mitchell, J. E. & McCall, F. C. Amer J Dis Child 106 207, 1963.

Nahmias, A. J. Naib, Z. M., Josey, W. E. & Clepper, A. C. Obstet Gynec 29 395, 1967.

Naib, Z. M., Nahmias, A. J. & Josey, W. E. Cancer 19 1026, 1966.

Nigogosyan, G. & Mills, J. JAMA 191 152, 1965.

Sharlit, H. Arch Dermat and Syph 42 933, 1940.

Slavin, H. B. & Gavett, E. Proc Soc Exp Biol Med 63 343, 1946.

Stern, E. & Longo, L. D. Acta Cytol 7 295, 1963.

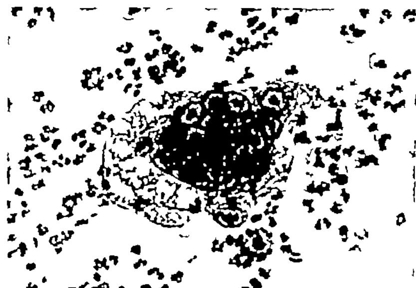


Fig 1 Photomicrograph showing a group of nuclei with inclusion bodies in a scanty cytoplasm. Papanicolaou stain, 76.

RESULTS

In samples from 5 patients a herpes simplex virus-like agent was isolated. One sample gave a cytopathogenic effect in both MASA and BS-C 3 tissue cultures. No attempt was made in this case to isolate virus on egg membranes. Two samples showed cytopathogenic effect on BS-C 3 cells only Two of the five samples gave pocks-like changes on the egg membranes. Positive tissue cultures gave invariably pocks on egg membranes and positive egg membranes could be passed to tissue cultures. The cytopathogenic effect in tissue culture and the pocks on the egg membranes were typical for herpes simplex virus However no attempt was made to distinguish between herpesvirus hominis antigenic type 1 and 2.

Cytological evidence of herpes simplex was found in smears from 11 of the women. The five above mentioned virological positive cases were all found among these 11 patients. Gynaecological examination revealed changes suggesting herpes genitalis in 3 of the women. All 3 showed cytological, and 2 of them also virological, evidence of herpes simplex.

Infection with gonococci and Trichomonas was almost twice as common in the cytologically positive group—36% and 45% respectively as in the entire series, where the corresponding figures were 21% and 24% respectively

The mean age was 25.5 years for the entire series and 29 6 for the cytologically positive group. One of the women in the latter group was menopausal. There was no obvious relation between the phase of the menstrual cycle and the clinical



Fig Photomicrograph showing typical syncytium. Papanicolaou stain, 76.

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DIVERTICULA OF THE WALLS OF THE FALLOPIAN TUBES

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Abstract. The part played by genital tuberculosis, salpingitis isthmica nodosa and endometriosis tubae interna in the formation of diverticula of the Fallopian tube is discussed. The author supports the view that radiographic differential diagnosis between the latter two conditions is not possible. A case is described in which diverticulum of the middle portion of the Fallopian tube was revealed by hysterosalpingography in a patient, aged 28 years. She had a history of two episodes of salpingitis, two spontaneous abortions and of a tubal pregnancy on the right side which was treated by excision of the fimbriated end of the right tube. The radiographic appearance of the lesion did not resemble those of the diverticula seen in salpingitis isthmica nodosa, endometriosis tubae interna or genital tuberculosis. The genesis of the lesion could not be determined with certainty

Diverticula of the walls of the isthmic and intramural portion of the Fallopian tube are occasionally disclosed by hysterosalpingography. Genital tuberculosis, salpingitis isthmica nodosa and endometriosis tubae interna are said to account for these lesions. Each of these three conditions is a distinct clinical entity with characteristic histological features. In tuberculous salpingitis there are necrotic areas, tubercles and giant cells in the tubal wall. Salpingitis isthmica nodosa is a form of chronic salpingitis, the characteristics being small epithelium-lined cannals and small cavities in the middle portion of the tube. Inflammatory cells usually surround the small cavities. Canals and cavities are also seen in endometriosis tubae interna and histological examination shows the characteristic features of endometriosis. However the histological differential diagnosis may be difficult

This paper briefly describes a case of diverticulum of the wall of the isthmic portion of the tube, which was revealed by hysterosalpingography and which was apparently due to other factors than those discussed above. As such a case has so far not been encountered, to the best of the author's knowledge, it was considered to be of sufficient interest to be reported.

CASE REPORT

The patient, aged 28 years, was childless. She had a history of episodes of salpingitis, one in 1955 the other in 1959 two spontaneous abortions, the first in 1964 in the third month of pregnancy the second in 1965 in the second month of pregnancy and of a tubal pregnancy on the right side in 1966. This was treated by excision of the fimbriated end of the right tube. At operation, the middle portion of the tube did not show any abnormality. As the patient failed to conceive again thereafter hysterosalpingography was carried out. The findings were as follows: a tubo-ovarian cyst on the left side and failure of the opaque medium to pass into the abdominal cavity on this side, a diverticulum, about 4 by 8 mm in size, in the middle portion of the right tube, slight widening of the distal end of the tube being suggested (Fig. 1). Otherwise the right tube did not show any abnormality the opaque medium being seen to pass into the abdominal cavity

Two months later the patient had an operation consisting of removal of the middle portion of the right tube. At laparotomy a bluish, slightly glossy cystic swelling, approximately 1.5 cm in diameter was found about 1 cm from the right cornu. Pathological report: *Unilocular cystic swelling, the size of a bean, containing clear brown substance and lined with a single, fairly tall, columnar epithelium. Outside the latter there are concentrically arranged layers of fibro-muscular tissue, within which several cavities lined with the same type of epithelium as the cystic swelling are seen. Some of the small cavities appear to be continuous with the cystic swelling. There is no evidence of inflammation, malignancy or retained debris of ovum.*

In order to look for a similar case, 4360 abnormal hysterosalpingograms from the Radiological Department of the Karolinska Hospital were

Stich, H. F. Hsu, T. C. & Rapp, F. Virology 439 1964
Varga, A. & Browell, B. Obstet Gynec *16* 441 1960.
Yen, S. S. C., Reagan, J. W. & Rosenthal, M. S. Obstet Gynec 25 479 1965

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I order to look for a similar case, 4360 abnormal hysterosalpingograms from the Radiological Department of the Karolinska Hospital were



Fig 1 Hysterosalpingogram on a oman aged 8 years. A diverticulum, 4 by 8 mm in size is shown in the middle part of the right tube

reviewed. The hysterosalpingograms reported as normal, were not re-examined because it was considered to be most unlikely that a lesion of the size described here could have escaped attention.

In 50 cases there was definite radiographic evidence of diverticulosis, but in none of these cases did the findings resemble those in the case reported here. It should be mentioned, however that some of the radiographs from which tuber culous salpingitis had been diagnosed, were not available for re-examination.

In 12 of these 50 cases the specimen removed at operation was examined histologically but only in 7 did the examination include the part of the tubal wall showing diverticula. In a further 3 cases only curettage was performed. As the curet tings showed histological evidence of tuberculosis these cases were included because it has been demonstrated that the tubes also show tuberculous in virtually 100 % of cases (Novak & Novak 1958)

Thus, the conditions accounting for the tubal lesions were diagnosed in 10 cases, being salpingitis isthmica nodosa in 4 cases, endometriosis tubae interna in 2 cases and tuberculosis in 4 cases.

DISCUSSION

The radiographic appearance of the diverticulum disclosed by hysterosalpingography in the case reported here differed from that of the diverticula seen in salpingitis isthmica nodosa (Fig.), endometriosis tubae interna (Fig. 3) and genital tuber culosis (Fig. 4)

In the presence of these conditions there usually are several small diverticula with a diameter of 1–_ mm whilst in the case described here there was radiographic evidence of only one irregularly outlined diverticulum measuring about 4 by 8



Fig   Hysterosalpingogram on   woman aged 34 y rs. Numerous small diverticul in the   th f the middle portions f both tubes re shown Histological diagnosis. Salpingitis isthmica nodosa



Fig 3 Hysterosalpingogram on a oman aged 31 years Numerous small diverticula in the walls of the middle portions of both tubes are shown Histological diagnosis Endometriosis tubae internae.

mm The factors involved in the formation of the lesion could not be determined It is interesting to not that the middle portion of the right tube was considered to be normal at the first operation which was performed six months before the sec ond This suggests that the lesion developed comparatively rapidly

The number of cases studied is too small to permit any firm conclusion about whether or not adiographic differential diagnosis between salpingitis isthmica nodosa and endometriosis tubae interna is possible However the findings support the view expressed by Madsen (1943) that the adiographic findings do not enable a differential diagnosis between these conditions to be made

Di erticula of the tubal walls may also be seen in genital tuberculosis. However the radiographic appearances are not sufficiently characteristic t enable the diagnosis of the disease to be made

The criteria suggested by Ekengren (1955) proved to be of value in the radiographic diagnosis of this condition.

Fig. 1 shows that the radiographic appearance of the lesion observed in the case discussed here differed from the ppearances f the diverticula shown in Figs 2–4 The factors involved in the formation of the lesion could not be determined.

This type of lesion appears to be rare as the case described here wa the only one in the 4360 cases reviewed.

REFERENCES

Ekengren, K Acta radiol, Suppl. 123 1955
Frankl, O Arch Gynak 135 556, 1928 29
Madsen, V Acta obstet gynec scand 23 353, 1943
Novak, E. & Novak, E Gynecologic and Obstetric Pathology 4th ed Saunders, 1958.



Fig 4 Hysterosalpingogram on oman aged 42 years Small diverticula in the all of the middle portion of the right tube are how Histological diagnosis Genital tuberculosis



Fig. 1. Hysterosalpingogram on a oman aged .8 years. A diverticulum, 4 by 8 mm in size is shown in the middle part of the right tube.

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DISCUSSION

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In the presence of these conditions there usually are several small diverticula with a diameter of 1–2 mm whilst in the case described here there was radiographic evidence of only one irregularly outlined diverticulum measuring about 4 by 8



Fig. Hysterosalpingogram on woman aged 34 years. Numerous small diverticula in the walls of the middle portions of both tubes are shown. Histological diagnosis. Salpingitis isthmica nodosa

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MICROBODIES IN TISSUE CULTURES FROM HUMAN CERVICAL CARCINOMAS

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Abstract. Tissue from 35 patients with invasive squamous-cell cancer of the cervix uteri at different clinical stages was transplanted intraperitoneally in 300 diffusion chambers into 300 castrated and non-castrated female rats.

The chambers were removed within 10 days. The contents of the chambers were fixed in 5% formalin and subjected to the usual methods of histological preparation, with staining by haematoxylin-eosin. Filters with tissue cultures were fixed in 95% ethanol and then stained with haematoxylin-eosin.

The cultures were found to contain growth of epithelial and stroma elements. The epithelial proliferation was found to be increased in the neighbourhood of the fibroblasts. The rate of proliferation did not depend on the clinical stage of the cancer.

Microbodies or blebs were found around the cell nucleus in varying numbers. The greatest number was found in cancer from clinically advanced cases. The nature of these microbodies has not been clarified, but they are in the course of being investigated.

The encouraging results obtained by Algire (1956), Weaver et al. (1955) with homograft transplantations in diffusion chambers have led to several transplantation experiments using this technique, in homologous as well as heterologous systems.

The membranes in the diffusion chambers provide protection against the invasion of cellular elements, but permit the diffusion of proteins and electrolytes. Subsequent experiments with the transplantation of endocrine tissue have shown that in the diffusion chambers, within a limited period this tissue is able to produce hormones (Brooks & Hill, 1960; Castellanos & Sturgis, 1958; Lin et al. 196-; Potter & Haverback, 1960; Sturgis et al. 1958). There is a variation in the survival time of tissue from different organs. The reasons for this vary: one of them is presumably the progressive undernourishment of the transplant with time, *due to failure of the diffusion through* the filters. For the purpose of morphological studies, therefore, the author chose a period of approximately 10 days for the duration of the transplant in the host organism, and obtained good results in the transplantation of normal portio epithelium into female rats (Kurz, 1966).

The present report concentrates on the results with tissue obtained from invasive cervical carcinoma.

[1] The experiments were started at the Hormone Laboratory, Dept. of Obst. & Gyn. (Professor Stig Kullander M.D.), Malmö General Hospital, University of Lund, Malmö, Sweden.

MATERIAL AND METHOD

Thirty-five patients with histologically verified invasive squamous-cell cancer of the cervix uteri were chosen for the transplantation experiments. In these patients, the carcinoma was classified clinically and surgically into stages I to III, according to the international classification. None of the patients had previously received radium therapy or treatment with cytotoxic drugs. All patients in stage I, a total of 16, underwent Wertheim radical operation. In these cases, tissue was removed for transplantation with sterile precautions in the operating theatre, after removal of the uterus. In the other patients, the tissue was obtained from the portio by biopsy performed in the operating theatre, according to the usual methods. Immediately after removal of the tissue, it was placed in sterile Ringer-Glucose solution to which penicillin and streptomycin had been added.

Sterilized diffusion chambers constructed from Millipore Filter (MF) membranes attached to 2 rings, and with a pore size of 0.45 μ, were placed in sterile Petri dishes. The tissue was dissected out in small fragments (chamber volume approx. 1 ml) and placed on the MF membrane fastened to the larger of the two rings. The chamber was then closed by means of a slightly smaller ring to which a membrane had been attached. Both rings were then sealed with MF cement, and the chamber

Philipp, E. & Huber H. Zentralbl für Gynäkologie 68 69 1944
Seitz, L. & Amreich, F. Biologie und Pathologie des Weibes, 2nd ed., p. 170 Urban & Schwartzenberg, 195 –1955

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The localization of the fibroblasts in the neighbourhood of proliferating epithelial cells of basal cell type, imparted an organic structure to the tissue in the cultures. In such cases, epithelial cells formed a sheet consisting of one or more cell layers. A further mode of growth was found, where the fibroblasts were displaced by small undifferentiated cells. These undifferentiated cells, together with epithelial islets or isolated epithelial cells, formed a reticulum with which long out growths were associated.

The cultures obtained in non-castrated female rats were in general more suitable for morphological studies. These results could not be correlated with the ge of the patient and the clinical stage of the cancer at this time. A subsequent study will deal with the possibility of hormonal influence on epithelial proliferation and differentiation in the diffusion chambers.

The epithelial cells in the cultures were charac terized by polymorphism, hyperchromatism f the nuclei, abnormal nucleus/plasma ratio, chromosome breaks and abnormal mitotic figures.

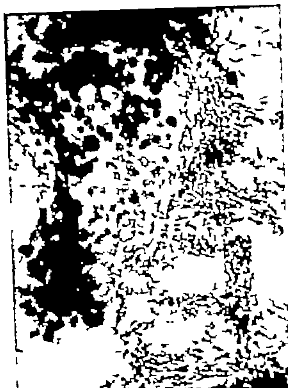


Fig. 4. Same culture epithelial proliferation in close association with proliferating fibroblasts (low power)



Fig. 3. 7-day-old culture in castrated rat (low power).

All the criteria f malignancy in epithelial cells, familiar from cytology can be recognized in the cultures.

In the present report the observation of microbodies around the nuclei in epithelial cells will be emphasized although the formation mechanism and fate of these bodies is unknown.

In giant cells with ill-defined protoplasmic boundaries, and with nucleus showing a honey combed or coarse chromatin structure with one or several nucleoli, the nucleoplasm is seen to be surrounded by small bodies or blebs. They appear in varying numbers at the cell nucleus, but can be so numerous that they form kind of ring or corona around the nucleus.

The greatest numbers have been found so far in cultures from clinically advanced cervical cancer but few have also been found in cases of clinical stage I.

I magnitude, these bodies or "blebs lie in the microscopic range which is clearly visible with the immersion objective, and consist of plasma-



Case 1 (*Figs 1–9*) 55-year-old patient with cancer of the uterine cervix stage II. Histologically: baso-cellular carcinoma with spino-cellular differentiation locally

Fig. 1 Biopsy material from the portio used for transplantation (low power magnification).

implanted intraperitoneally in female rats. The tissue from 35 patients was transplanted in 300 diffusion chambers in 300 female ts (one chamber per rat). In the series from one patient, f cast ted rats (ppr x 700 g) were ailable one half of the transplantations were made into these and the other half w re made int non castrated rats (approx 150 g). The entire proces was completed w thin hours

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The same technique as reported previously was used in the transplantation f normal po io epithelium (Kurz, 1966)

RESULTS

The transplants from 35 patients with invasive squamous-cell cancer of the cervix uteri produced growth in all cases but in varying degrees.

On opening the chambers, the actual implant was found to be more or less necrotized, but the structure could still be recognized. The greater part of the round cell infiltration remained in the implant

A tissue culture was found on the inner side of the filters containing growth of epithelial and stroma elements, either as continous sheets of cells in one or more layers with a certain degree of organic structure, or in a reticular arrangement with isolated epithelial islets or cells.

The proliferation, the epithelial differentiation and the distribution of the epithelial e ements and the stroma cells were d termined by the tissue structure in the transp ant. Good correlation was found between the fixed cultures and the tissue sections from the biopsy material

In cases of small invasive cancer processes it was of importance to perform larger transplantation series of tissue from one patient to avoid an incorrect impression of the proliferation and epithelial differentiation of the individual cancer. The fibroblast proliferation was found to be most pronounced in these cultures. In the clinically advanced stages of cervical cancer varying degrees of fibroblast proliferation were found.

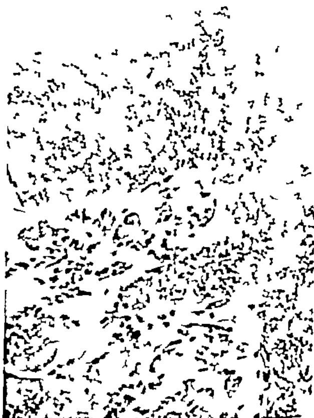


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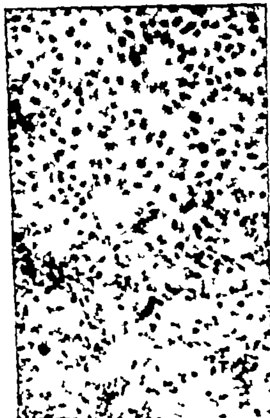
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Fig. 2 7-day-old transplant in castrated rat (low power magn ficati)



DISCUSSION

In an attempt to gain insight into events leading to neoplasia of the human cervix uteri, tissue from 35 patients with invasive squamous cell cancer at different clinical stages has been transplantated intraperitoneally in diffusion chambers into female rats. Thereby a tissue culture has been achieved "in vivo" over a limited time interval. In the diffusion chambers the transplant finds itself in a more physiological milieu. These conditions cannot be re-created in vitro. In vitro the cervical carcinoma shows a tendency to grow vigorously in the first days, but soon after the early extensive growth degeneration becomes evident (Kratochwil et al., 1965 Moore, 1952)

In the diffusion chambers the cultures were found to contain growth of epithelial cells and stroma elements with a certain degree of organic structure. The epithelial proliferation and differentiation was found to be increased in the neigh-

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Case 2 (Figs. 10–12). 38-year-old patient with cancer of the uterine cervix stage III, mainly intracervical. Biopsy material from portio. Histological examination: basocellular carcinoma with parakeratosis locally.

Fig. 10. 7-day-old culture in non-castrated rat (low power).

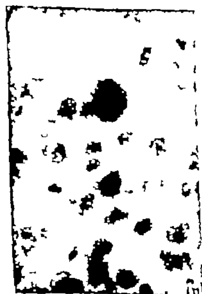




Fig. 11. Nucleus with "microbodies" (high power).

Fig. 12. The same as Fig. 11 (immersion).



Figs. 5–6 Giant nuclei with microbodies from culture in Fig. 3 (immersion).

like body and a dense and intensively stained centre. The body may be round, oval or pear shaped, and in the last case the small end points towards the nucleus. At times these bodies appear to be attached to the nuclear membrane by means of a filiform process.

If a connection with the nucleus cannot be seen under the microscope, the impression is gained that the bodies are in the process of withdrawing from the nucleus. The large nuclei are always in the resting phase and in the culture they lie peripheral to sites where mitoses are taking place. Occasionally there is a single round cell in the neighbourhood. These giant nuclei are relatively easy to locate in the cultures, if only on account of their size and their intense staining with haematoxylin-eosin.

The nature of these microbodies has not been clarified, but they are in the course of being investigated.



Figs. 7–9 Microbodies around nuclei from culture in non castrated rat (immersion).



DISCUSSION

In an attempt to gain insight into events leading to neoplasia of the human cervix uteri, tissue from 35 patients with invasive squamous cell cancer at different clinical stages has been transplantated intraperitoneally in diffusion chambers into female rats. Thereby a tissue culture has been achieved in vivo over a limited time interval. In the diffusion chambers the transplant finds itself in a more physiological milieu. These conditions cannot be re-created in vitro. In vitro the cervical carcinoma shows a tendency to grow vigorously in the first days, but soon after the early extensive growth degeneration becomes evident (Kratochwil et al., 1965; Moore, 1952).

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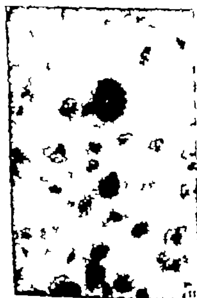
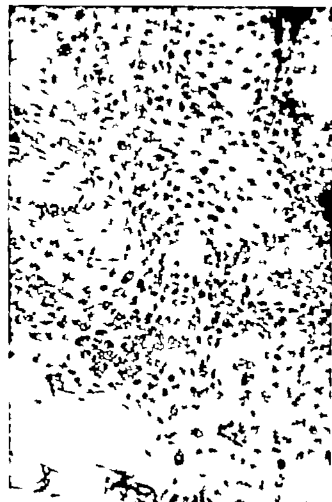




Fig. 11. Nucleus with microbodies (high power).

Fig. 12. The same as Fig. 11 (immersion).



bourhood of fibroblasts. The role of fibroblasts in tissue cultures has not yet been clarified but is undoubtedly of great significance.

The microbodies or blebs found around the cell nucleus are in the microscopically range in these cultures.

Projection of nuclear material has been reported in certain chromosome abnormalities (Atkin & Baker 1964). In cervical neoplasia an abnormal interphase chromosome marker in the form of a nuclear protrusion has been described (Uyeda et al. 1966). Abnormal (marker) chromosomes have been identified in cases with epidermoid carcinoma of the cervix (Jones et al. 1967, Wakonig-Vaartaja & Hughes 1965). As yet no firm conclusions can be drawn, whether the chromosomal changes are primarily responsible for the malignancy or are secondary to it.

Protrusions of the interphase nuclei do not

Case 3 (*Figs. 13–15*). 53-year-old patient with cancer of the uterine cervix stage I. Wertheim's radical operation. Histological examination: undifferentiated or slightly differentiated carcinoma. Squamous cell carcinoma.

Fig. 13. 7-day-old tissue culture in non-castrated rat (low power).

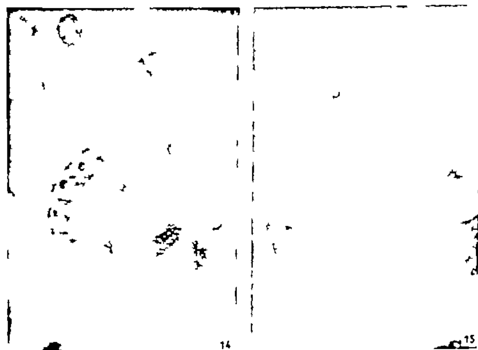


Fig. 14–15. Nuclei with bleb formations in same culture (immersion).

necessarily imply the presence of abnormal chromosomes.

Small blebs, which appear to arise by extrusion of the nuclear envelope and nucleoplasm, were observed in human leukemic cells and Burkitt lymphoma cells (Achong & Epstein, 1966 Ahearn et al., 1967 McDuffie 1967).

Ultrastructural examinations of these blebs revealed cytoplasmic material with mitochondria and centrioles within them.

Electron microscope examination of stained material from lymph nodes and bone marrow of leukemic patients has demonstrated the presence of structures resembling virus particles in the cytoplasma, elementary bodies of mycoplasma and mycoplasma at different size (Dmochowsky et al 1965).

The relationship between viruses and cancer has drawn attention to the genital herpes simplex infection in the female. There has been found atypical squamous epithelial alterations in the cervix with herpetic cellular changes. It has been suggested that the herpes simplex, DNA virus plays a role in the development of cervical cancer. Microscopical examinations of herpes simplex virus infected cells have revealed intranuclear inclusions (Josey et al., 1966).

An extreme proliferation and plication of the nuclear membrane with membranous projections containing virus particles has been observed in tissue cultures from an established human epidermoid cancer cell line (HE p2) infected with herpes virus hominis (Shipkey et al., 1967).

Attention has also been drawn to mycoplasma, PPLO as an cytopathic agent.

In genital infections the PPLO organisms have been found, by cultural methods, associated with cervicitis, vaginitis and urethritis in women. It was found that women carry PPLO much more frequent than men, and that these bodies are likely to be transferred by sexual intercourse (Klieneberger Nobel 1959).

Epidemiological studies and demographic data implicate an infective agent in the etiology of human cervical neoplasia.

The purpose of this paper is mainly to direct the attention to this transplantation technique for tissue from female genital organs and to demonstrate the presence of microbodies around nuclei in tissue cultures which so far has only been observed in cervical carcinomas. The author's observations are based on experience with 500 transplantations with tissue from different regions of the female genital organs from patients with benign and malignant gynaecological diseases.

ACKNOWLEDGEMENTS

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REFERENCES

Achong, B. G. & Epstein, M. A. J Nat Cancer Inst 36 877 1966.
Ahearn, M. J. Lewis, C. W. Campbell, L. A. & Luce, J. K., Nature (Lond) 15 196, 1967.
Algire, G. H. Transplant Bull 3 74 1956.
Atkin, N. B. & Baker M. C. Acta Cytol 8 431, 1964.
Brooks, J. R. & Hill, G. J. Amer J Surg 99 588 1960.
Castellanos, H. & Sturgis, S. H. Surg Forum 8 494, 1958.
Dmochowsky L., Taylor H. G. Grey C. E., Dreyer D. A. Sykes, J. A. Langford, Ph. L., Rogers, T. Shullenberger C. C. & Howe, C. D. Cancer 18 1345 1965.
Jones, H. W. Katayama, K. P. Stafl, A. & Davis, H. J. Obst & Gyn 30 790 1967.
Josey W. E., Nahmias, A. J. Naib Z. M., Utley P. M. McKenna, W. J. & Coleman, M. T. Amer J Obstet Gynec 96 493, 1966.
Klieneberger-Nobel, E. Brit Med J 1 19 1959.
Kraatschmal, A., Hoorn, E. & Holzner, H. Arch Gynäk 200 321, 1965.
Kurz, L. J Obst Gynec Brit C'lth 73 472, 1966.
Lin, T. Vanicka, A. & Lin, B. Plastic & Reconstr Surg 30 8, 1962.
McDuffie, N. G. Nature (Lond) 214 1341 1967.
Moore, J. G. Amer J Obst & Gynec 64 13, 1952.
Potter J. F. & Haverback, C. Z. Ann Surg 131 460 1960.
Shipkey F. H. Erlandson, R. A. Bailey R. B. Babcock, V. I. & Southam, Ch. M. Exper & Mol Pathology 6. 39 1967.
Sturgis, S. H. Castellanos, H. & Rahilly J. Amer J Obst & Gyn 76 1132, 1958.
Uyeda, C. K. Davis, H. J. & Jones, H. W. Acta Cytol 10 331, 1966.
Wakonig-Vaartaja, R. & Hughes, D. T. Lancet 2, 756, 1965.
Weaver J. M. Algire, G. H. & Prehn, R. T. J Nat Cancer Inst 15 1737 1955.

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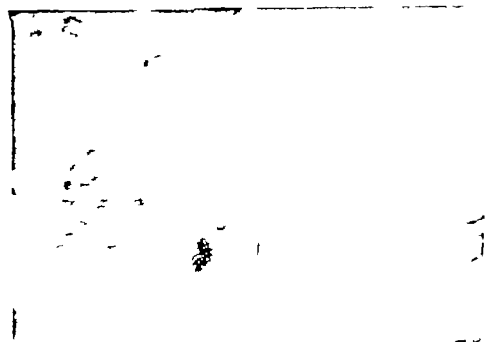
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Fig. 13. Colony tissue culture in [illegible] low power.



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REFERENCES

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Algire, G. H. Transplant Bull *3* 74, 1956.

Atkin, N. B. & Baker M. C. Acta Cytol *8* 431, 1964.

Brooks, J. R. & Hill, G. J. Amer J Surg 99 588, 1960.

Castellanos, H. & Sturgis, S. H. Surg Forum *8* 498 1958.

Dmochowsky L., Taylor H. G. Grey C. E. Dreyer D. A. Sykes, J. A. Langford, Ph. L., Rogers, T. Shullenberger C. C. & Howe, C. D. Cancer *18* 1345 1965.

Jones, H. W. Katayama, K. P. Stafl, A. & Davis, H. J. Obst & Gyn *30* 790, 1967

Josey W. E., Nahmias, A. J. Naib, Z. M., Utley P. M. McKenna, W. J. & Coleman M. T. Amer J Obstet Gynec 96 493 1966

Klieneberger-Nobel, E. Brit Med J *1* 19 1959

Kratochwil, A. Hofmann, E. & Holzner H. Arch Gynäk *200* 321, 1965

Kurz, L. J Obst Gynaec Brit C'lth *73* 472, 1966

Lin, T. Veselka, A. & Lin, S. Plastic & Reconstr Surg *30* 8, 1962

McDuffie, N. G. Nature (Lond) *214* 1341 1967

Moore, J. G. Amer J Obst & Gynec 64 13, 195_

Potter J. F. & Haverback, C. Z. Ann Surg *151* 460 1960

Shipkey F. H., Erlandson, R. A. Bailey R. B., Babcock, V. I. & Southam, Ch. M. Exper & Mol Pathology 6 39 1967

Sturgis, S. H. Castellanos, H. & Reboldy J. Amer J Obst & Gyn *78* 1132, 1958

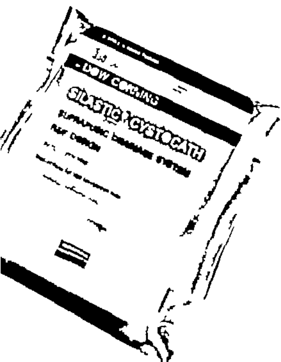
Uyeda, C. K. Dean, H. J. & Jones, H. W. Acta Cytol *10* 331, 1966

Wakonig Vaartaja, R. & Hughes, D. T. Lancet 2 756, 1965

Weaver J. M. Algire, G. H. & Prehn, R. T. J Nat Cancer Inst *15* 1737 1955

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RECURRENT CHOLESTASIS OF PREGNANCY

Treatment with Cholestyramine of one Case with an Unusually Early Onset

J. Engström, K. Hellström, N. Posse and J. Sjövall

From the Department of Internal Medicine, Serafimer Hospital (Head, Professor G. Biörck, M.D.), the General Maternity Hospital (Head L. Lindgren, M.D.), and the Department of Chemistry, the Caroline Institute (Head Professor S. Bergström, M.D.), Stockholm, Sweden

Abstract This report of 28-year-old woman with cholestasis occurring in the first month of gestation in four consecutive pregnancies. During the interval between the third and fourth pregnancy as well as during and after the fourth one the patient was regularly examined with regard to her liver function. Intensive itching and markedly elevated serum bile acids were the predominant symptom and laboratory finding during the fourth pregnancy. Both decreased during cholestyramine treatment. The bromsulphalein retention was quite normal six months after the third pregnancy but was still elevated two and half years after the last one.

In pregnancy two groups of hepatic disturbances with jaundice have been described: jaundice that is unique to the pregnant woman and jaundice caused by other conditions complicating the pregnancy. The former group includes the very rare condition originally described by Sheehan (1940) as obstetric acute yellow atrophy and recurrent cholestasis of pregnancy. The latter condition has been described by many synonyms for instance recurring idiopathic jaundice of pregnancy (McAllister & Waddell, 1962), hepatosis of pregnancy (Arfwedson, 1953) and jaundice in late pregnancy (Thorling, 1955). The predominant symptoms are pruritus and icterus, which usually develop during the last trimester of the pregnancy and disappear shortly after delivery. The itching is often severe, whereas the jaundice is mild. The laboratory findings, with elevation of serum alkaline phosphatase and, as a rule, negative flocculation and turbidity tests are in agreement with the cholestasis seen in liver biopsy specimens.

It has been suggested that an elevation of bile acids in blood may be responsible for the itching in hepato-biliary diseases. Recent studies have supported this hypothesis in so far that patients with biliary cirrhosis as well as pregnant women with itching seem to have an elevation of serum bile acids (Datta & Sherlock, 1963; Sjövall & Sjövall, 1966). According to several reports the pruritus of biliary cirrhosis has been successfully treated with cholestyramine, an anionic resin exchanger with a special affinity for bile acids (Hashim & van Itallie, 1960; Datta & Sherlock, 1963; Kecskes et al., 1964). Brown et al. (1963) and Fast & Roulston (1964) gave cholestyramine to two pregnant women and in both cases the itching disappeared.

A case of recurrent itching and jaundice in four consecutive pregnancies is reported in this paper. The onset of the symptoms in each pregnancy was extraordinarily early. During the last pregnancy the serum bile acids were studied before and during treatment with cholestyramine.

CASE HISTORY

The patient was 28-year-old housewife, who was in good health, except during the pregnancies. On few occasions she had been treated with vitamin injections because of tiredness. There was no family history of liver disease. The patient had not been exposed to hepatitis or hepatotoxic drugs as far as is known. She came into our care during the interval between the third and fourth pregnancy.

First pregnancy

The patient was pregnant for the first time at the age of 22. Pruritus, pale stools and slight jaundice developed at the end of the first month and persisted during the rest of the pregnancy. In addition she had several attacks of abdominal pains and nausea. There was persistent dull ache in the right upper abdomen. The



Fig 1 Liver biopsy specimen, second pregnancy Original magnification, 40. Haematoxylin and eosin staining.

pains were interpreted a biliary colic. No laboratory data concerning the liver function during this period are allable. At the end of the 8th month she was delivered of a child (eight 450 g), that had died before labour The body showed general maceration, rupture of the cerebellar tentorium, subdural as well as leptomeningeal bleeding. The mother recovered rapidly after the delivery On the fourth day the icteric index was 1 10 and shortly thereafter the itching disappeared complet ly Cholecystography in the late puerperium re ealed several stones in the gall-bladder

Second pregnancy

Three months after the first delivery the patient became pregnant again. Pruritus, icterus, pale stools and attacks of abdominal pain reappeared during the first month. The abdominal pains were of the same character as during the first pregnancy Cholecystectomy was per formed t the beginning of the third month. The h er was found t be firm but of normal size The gall-bladder contained several small stones and showed cholesterosis but no cholecystitis. Cholangiography showed no evidence of biliary obstruction. Microscopic examination of a biopsy specimen (Figs. 1 and 2) revealed normal acinar structure in the liver Many parenchymal cells were loaded with pigment but seemed therwise normal as did the Kupffer cells. The bile canaliculi were dilated and rich in bile thrombi. The connective tissue of the portal areas was sparsely infiltrated with leucocytes. Jaundice and pruritus disappeared after the operation but reppeared within three months. At the end f the 8th month the icteric index was 1 27–1 3 She as delivered of a normal child (weight 1920 g) in the 36th week after digital dilatation of the cervix. Icterus and pruritus disappeared within 3 eeks. On the 6th and 12th day of the puerperium the icteric index was 1 18 and 1 10 respectively No further liver function tests were performed.

Third pregnancy

The third pregnancy started when the patient was 4 ears old. Icterus, pale stools and pruritus appeared as

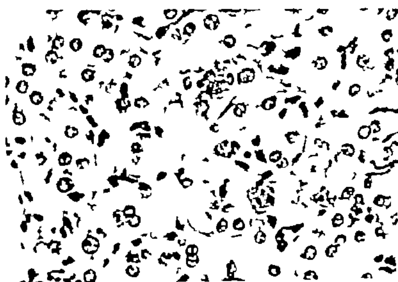


Fig Li er biopsy specimen, second pregnancy Original magnification, 600 Haematoxylin and eosin staining.

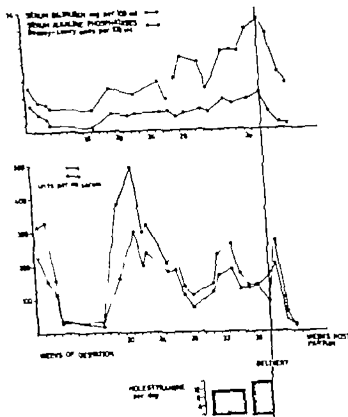


Fig 3 Serum bilirubin, alkaline phosphatase, GOT and GPT during the fourth pregnancy

primary symptoms of pruritus in the end of the first month. 3 weeks later the serum bilirubin was 3.9 mg%. During this pregnancy she had no abdominal pains. The pruritus increased progressively and became almost unbearable by the end of the third month. At that time the patient was in such a bad condition that legal abortion was induced. During the next four days the icteric index decreased from 1 30 to 1 19 but slight jaundice and pruritus persisted for about four weeks.

Two months after the operation the patient was admitted to the medical department. Physical examination revealed no abnormality. Haemoglobin, red and white cell counts, reticulocytes, thrombocytes, osmotic fragility of erythrocytes, sedimentation rate and serum creatinine were normal. Qualitative tests for urobilinogen, urobilin, protein and sugar in the urine were normal. Serum iron was 58 µg per 100 ml, serum bilirubin was 1.1 mg%. Alkaline phosphatase, thymol turbidity, S GOT and S GPT ... than the normal range as was the prothrombin-... index. Electrophoresis of serum proteins showed slight elevation of the beta- and gamma fractions (1 09 and 1 67 g% respectively). Serum fibrinogen and haptoglobin were normal. The retention of bromsulphalein (BSP ... mg/kg body weight) was 14.2 and 9.5% after 30 and 45 min respectively ... pathological values. X-ray examination showed normal size of liver and spleen. Intravenous cholangiography did not reveal any abnormality. The BSP test was repeated 10 months post partum and normal results were found (6 and 3% retention after 30 and 45 min respectively).

Fourth pregnancy

There were no symptoms of hepato-biliary disease during the two and a half year interval between the third and fourth pregnancy. The first evidence (itching) of her new pregnancy developed in the third week. The pruritus progressed rapidly and was accompanied after some days by jaundice and acholic faeces. On admittance to the hospital in the sixth week she was in good condition but complained of insomnia, which in her opinion was due to the itching.

Physical examination revealed ... slight icterus and numerous scratch marks especially on the extremities. The liver and the spleen were not palpable. Blood pressure was 125/80. Laboratory data were compatible with bile stasis, serum bilirubin 3.0 mg%, alkaline phosphatase 5.2 units (Bessey–Lowry units), thymol turbidity 0.5 units, S GOT 225 and S GPT 315 units (Karmen units) (Fig. 3). Bile acids in the blood were markedly elevated (Fig. 4). The concentration of cholic acid, chenodeoxycholic acid and deoxycholic acid was 50.9, 21.7 and 4.5 µg/ml respectively. In the method used (Sandberg et al. 1965) the mean values for normal nonpregnant cases are: cholic acid 0.29 µg/ml (range 0.05–0.83), chenodeoxy-



Fig 1 Li er biopsy specimen, second pregnancy Original magnification, 40. Haematoxylin and eosin staining.

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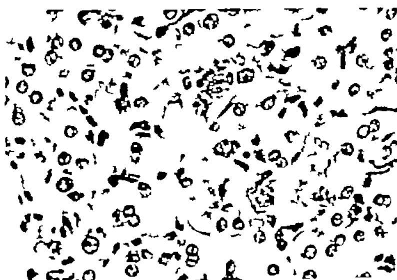


Fig Liver biopsy specimen, second pregnancy Original magnification, 600 Haematoxylin and eosin staining

DISCUSSION

Recurrent cholestasis of pregnancy is a disease entity characterized by (1) laboratory data and a histological picture compatible with intrahepatic cholestasis, (2) rapid disappearance of symptoms after delivery and (3) a marked tendency to recurrence in subsequent pregnancies.

In the majority of cases the symptoms start late in the pregnancy but there are exceptions. Haemmerli (1966) summarized the literature and separated the 132 reported cases of recurrent jaundice into several groups, according to the accuracy with which the diagnosis was recorded. In one group of 18 patients, who underwent 70 gestations the diagnosis was based both on liver biopsies and adequate laboratory data. The full syndrome with pruritus and jaundice occurred in 47 of the pregnancies. The mean onset of jaundice in these patients was in the 26th week of gestation, and the observed range varied between the 7th and the 39th week. In another group of 37 icteric pregnancies no biopsies were performed, but the diagnosis was confirmed by laboratory data. In five of these cases the onset of jaundice was in between the 10th and the 16th week, whereas in the rest the icterus started later on in the pregnancy. One case with a very early onset was reported by Schwalm (1932), who had a patient that became icteric in the first month of all her 12 pregnancies. Unfortunately however the diagnosis was not accurately confirmed by laboratory data.

It seems to be the general experience that patients with recurrent cholestasis of pregnancy are in good condition in spite of the disturbed liver function. Post delivery pruritus and jaundice disappear rapidly and there is no evidence so far that the cholestasis is followed by residual damage to the liver. Our patient had an extraordinarily early onset of symptoms in all her four pregnancies but otherwise the manifestations of her disorder were those usually encountered in other women with cholestasis of pregnancy.

The biopsy findings support the diagnosis in so far that there was a marked cholestasis. There was also moderate infiltration of leucocytes in the portal tracts which is not typical of cholestasis of pregnancy. However the biopsy specimen was obtained during the second pregnancy and the simultaneous occurrence of cholelithiasis might have influenced the histological picture.

In all instances the itching and jaundice disappeared and the serum bilirubin and alkaline phosphatase became normal early in the puerperium. After the third delivery the BSP retention was abnormal in the third month but normal in the sixth month, whereas after the fourth pregnancy the test was still abnormal two and a half years post delivery. This indicates either that the recovery of the liver is extremely slow after the last pregnancy or that the patient has got a residual liver damage.

In recent years several investigators have reported a striking resemblance between recurrent cholestasis of pregnancy and the cholestasis induced by some hormonal drugs, such as ovulation inhibitors and C-17-α-alkyl substituted testosterones. Since cholestasis of pregnancy usually develops late in the pregnancy when the production of oestrogens and progesterone is high it is tempting to speculate whether these two types of cholestasis may be triggered by the same mechanism. Reports of cholestasis caused by ovulation inhibitors in women with previous cholestasis of pregnancy may support this hypothesis (Adlercreutz, 1964, Ikonen, 1964). However as pointed out by Haemmerli the two disorders differ in many respects. Thus the jaundice in the drug induced cholestasis may be very marked whereas icterus is mild in cholestasis of pregnancy. The latter disorder has no prodromal symptoms whereas a period of fever, anorexia and malaise is often noticed before cholestasis induced by drugs. The symptoms in our patient developed at a time when the production of the female hormones is supposed to be within the normal range. During two of the pregnancies there was a marked improvement in the third month. This occurred spontaneously in the fourth and after cholecystectomy in the second pregnancy. Whether these changes are related by some means to alterations in hormonal production is not known. Repeated urinary analyses of pregnandiol, oestriol, oestrone and the 17-keto- and 17-hydroxysteroids in each instance showed ordinary results.

The patient's predominant symptom during the whole pregnancy was the itching. It was reduced during cholestyramine treatment but did not disappear. At the same time the serum bile acids dropped, but were still elevated, probably because of the marked stasis in the bile canaliculi, which also produced acholic faeces. The only complica-

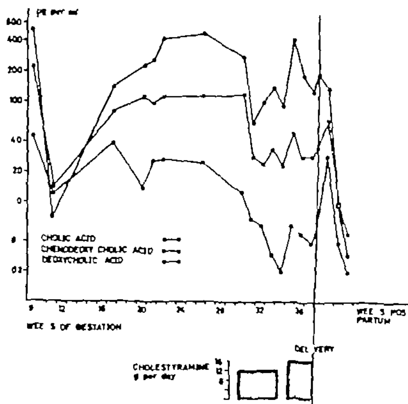


Fig 4 Serum bile acids during the fourth pregnancy

cholic acid 0.30 μg ml (0 08–0 66), deoxycholic acid 0.28 g ml (0.08–0.93) and total bile acids 0.87 μg/ml (0 4–1 65).

There was n anaemia (haemoglobin 12.7 g%, and serum iron 133 μg) and no evidence f renal disease (serum creatinine 0 80 mg% normal standard urine analyses). Bleeding time coagulation time thrombocyte counts were normal as well as white cell counts and sedimentation rate Serum lectrophoresis showed elevation of β-globulins (1.37 g%).

During the next 14 days the patient recovered spontaneously The serum bilirubin dropped to 0 7 mg% alkaline phosphatase to 2.7 units, S GOT and S.GPT to 31 and 37 units respectively The itching decreased simultaneously but did not disappear

After this period the patient was xamined t the outpatient clinic every second to third week. In addition she w s admitted to the hospital every second month for a more thorough examination. The improvement noticed bove continued at home and between the 12th and 16th week she was free from any symptoms The serum bilirubin, S.GOT and S GPT wer all normal t the end of the 16th week. Serum bile acids and alkaline phosphatase dropped too but did not reach normal values

The symptoms ppeared again in the 17th week of the pregnancy and during the next four weeks the pruritus was very intense and liver tests were as abnormal as when the patient was admitted t the hospital eight weeks earlier (Figs. 3 and 4). In spite of this her general condition was good At home she took care of most of her housework as well as f her three-yea -old daugther

Treatment with cholestyramine (12 g per day) was instituted in the 30th week. Electrolytes, prothrombin-proconvertin index, serum calcium and phosphorus and the liver function tests were followed almost once a week. After 5–7 days of treatment the patient noticed decreased itching, especially on the arms At the same time the bile acids fell by about 75% but were still far above normal values (Fig. 4). No changes were recorded in the bilirubin, alkaline phosphatase, transaminases, calcium or phosphorus in the serum.

Parenteral administration f 20 mg phytomenadion promptly normalized the prothrombin-proconverti index which fell from 100 to 70 on the 5th day of treatment. Cholestyramine therapy as stopped in the 34th eek, and this resulted in increased itching and elevation of the serum bile acids These changes were again reversed by administration f 16 g cholestyramine per day (Fig. 4) During the rest of the pregnancy 10 mg menadiol tetrasodium-diphosphate was gi en orally twice week and w th this therapy the prothrombin-proconvertin inde remained about 100 From now on the patient was lso given calcium (1 g Sandoz), folic acid (15 mg), ferrosuccinate (100 mg)

Labour was induc d in the 37th eek by artificial rupture of the foetal membranes The delivery followed after three hours and was uncomplicated. The weight of the child as 840 g Itching disappeared almost complet ly and bilirubin, transaminases and the serum bile cids became almost normal within four weeks (Figs. 3 and 4). At that time alkaline phosphatase was still abnormally elevated but became almost normal in the third month post delivery Repeated BSP tests during the following years all showed pathological alues The retention of BSP in the 15th month after delivery was 19 and 14 % after 30 and 45 min respectively On eexamination two and a half years post partum the corresponding values were 18 and 15%

APPARENT LACK OF OVARIAN OESTROGEN SYNTHESIS ASSOCIATED WITH OVULATION AND CORPUS LUTEUM FORMATION

K.-G. Tillinger, E. Johannisson, B. P. Lisboa, J. I. Raeside and E. Diczfalusy

From the Swedish Medical Research Council Reproductive Endocrinology Research Unit (Head, Professor E. Diczfalusy, M.D.), the Hormone Laboratory and the Department of Women's Diseases (Head, Professor U. Borell, M.D.), Karolinska Sjukhuset, Stockholm, Sweden

Abstract. A patient is described with primary amenorrhoea, elevated urinary pregnanediol and pregnanetriol and diminished aldosterone excretion and with clinical signs of hypooestrogenism, but without signs of virilization. Sequential stimulation by large doses of human menopausal and chorionic gonadotrophins resulted in the formation of several Graafian follicles and fresh corpora lutea. These morphological changes are not accompanied by any clinical signs of an increased oestrogen secretion or by an increased urinary oestrogen excretion. Tracer studies revealed that the patient was capable of carrying out 17α-hydroxylation, but not the removal of the steroid side-chain. It is concluded that ovulation and corpus luteum formation in women are not dependent on concomitant oestrogen synthesis by the maturing follicle.

It is generally agreed that follicle maturation in the human species is associated with an increased oestrogen synthesis by the ovary as reflected by proliferative endometrium, increased maturation of vaginal epithelial cells and increased urinary elimination of various oestrogen metabolites. It is also established that, when several follicles are brought simultaneously to maturation, for instance following stimulation with exogeneous gonadotrophins, the urinary oestrogen excretion becomes so exaggerated that it may reach mid-pregnancy levels (Gemzell et al., 1958; Diczfalusy et al., 1964). On the other hand, in all subjects in whom, following gonadotrophin stimulation, the endometrium remained atrophic, and no rise in urinary oestrogen excretion was found, it was invariably possible to establish the lack of functional ovarian tissue at subsequent laparotomy (Gemzell et al., 1959).

In view of these considerations, we thought it would be of considerable interest to report on subject in whom stimulation by human gonadotrophins resulted in multiple ovulation and in the subsequent formation of several corpora lutea, without any apparent signs of increased oestrogen synthesis.

MATERIAL AND METHODS

Trivial names: Systematic names

Aldosterone: 11β,21-dihydroxy-18-aldo-pregn-4-ene-3,20-dione
Androstenedione: androst-4-ene-3,17-dione
Androsterone: 3α-hydroxy-5α-androstan-17-one
Dehydroepiandrosterone: 3β-hydroxy-androst-5-en-17-one
Dexamethasone: 11β,17α,21-trihydroxy-16α-methyl-9α-fluoro-pregna-1,4-diene-3,20-dione
Epi-androsterone: 3β-hydroxy-5α-androstan-17-one
Etiocholanolone: 3α-hydroxy-5β-androstan-17-one
11β-hydroxy-etiocholanolone: 3α,11β-dihydroxy-5β-androstan-17-one
Iso-etiocholanolone: 3β-hydroxy-5β-androstan-17-one
Florinef (fluorocortisone acetate, fluorhydrocortisone acetate): 11β,17α,21-trihydroxy-9α-fluoro-pregn-4-ene-3,20-dione,21-acetate
Oestradiol: oestra-1,3,5(10)-triene-3,17β-diol
Oestriol: oestra-1,3,5(10)-triene-3,16α,17β-triol
Oestrone: 3-hydroxy-oestra-1,3,5(10)-trien-17-one
11-Oxo-androsterone: 3α-hydroxy-5α-androstane-11,17-dione
Pregnanediol: 5β-pregnane-3α,20α-diol
Pregnanetriol: 5β-pregnane-3α,17α,20α-triol
Pregnenolone: 3β-hydroxy-pregn-5-en-20-one
Tetrahydrocortisol: 3α,11β,17α,21-tetrahydroxy-5β-pregnan-20-one
Tetrahydrocortisone: 3α,17α,21-trihydroxy-5β-pregnane-11,20-dione
Tetrahydro-11-deoxycortisol: 3α,17α,21-trihydroxy-5β-pregnan-20-one

Gonadotrophins

Human menopausal gonadotrophin (HMG-B), batch no. P-25E318 was obtained from Istituto Farmacologico Se-

tion that could be related to treatment was the transient drop of the prothrombin proconvertin index. Urinary excretion of pregnandiol, oestrone, oestriol 17-hydroxy and 17-ketosteroids gave no evidence that cholestyramine interfered with the metabolism of the hormones mentioned.

It has been suggested (Haemmerli, 1966) that the prognosis after cholestasis of pregnancy is excellent. However only a few women have been observed for several years after delivery and it is not possible today to draw any definite conclusion with regard to the long term prognosis. The present status of our patient indicates that cholestasis of pregnancy under certain circumstances may be followed by chronic liver disease.

REFERENCES

Adlercreutz, H. Steroidbetingad ikterus. Nord Med 7? 1004 1964

McAllister J E & Waddell, J M Recurring idiopathic jaundice in pregnancy case report. Amer J Obst Gyn *84* 62, 1962.

Arfwedson, H. Graviditetsklåda. S Läkartidn *50* 1685 1953

Brown, D F Porta, E A & Reder J Idiopathic jaundice of pregnancy Arch Int Med *111* 59., 1963

Carey J B. Jr & Williams, G. Relief of pruritus of jaundice with bile acid sequestering resin. JAMA *176*. 43., 1962.

Datta, D V & Sherlock, S. Treatment of pruritus of obstructive jaundice with cholestyramine Brit Med J *1* 216, 1963

Fast, B. B. & Roulson, T M. Idiopathic jaundice of pregnancy Amer J Obst Gyn *88* 314 1964

Haemmerli, U P Jaundice during pregnancy Acta Med Scand *179* Suppl. 444 1966.

Hashim, S. A. & an Itallie T B. Use of bile cid sequestrant in treatment of pruritus associated with biliary cirrhosis. J Invest Derm *35* 53 1960.

Ikonen, E. Jaundice in late pregnancy Acta Obst Gyn Scand *43* Suppl. 5 1964.

Keczkes, K., Goldberg, D. M & Ferguson, A. G Xanthomatous biliary cirrhosis treated with cholestyramine. Arch Int Med *114* 3.1 1964

Sandberg, D H., Sjovall, J Sjövall, K. & Turner D A. Measurement of human serum bile acids by gas-liquid chromatography J Lip Res 6. 182, 1965

Schwalm, M. Rezidivierender Schwangerschaftsikterus. Zbl Gynaek *56*. 2098 1932.

Sheehan, H. L. The pathology of acute yellow trophy and delayed chloroform poisoning. J Obstet Gynaec Brit Emp *47* 49 1940.

Sjövall, K. & Sjövall, J Serum bile acid levels in pregnancy with pruritus. Clin Chim Acta *13* 207 1966.

Svanborg, A. A study of recurrent jaundice in pregnancy Acta Obst Gyn Scand *33* 434 1954

Thorling, L. Jaundice in pregnancy a clinical study Acta Med Scand *151* Suppl. 302, 1955

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Fig. 2. X-ray picture of the skull. Note the mandibular angle and the malformation of the nose

At the age of 33, she married a man aged 28. She was admitted now to the hospital because of infertility

Clinical findings

The patient displayed hypogonadic proportions with span of 172 cm and height of 167 cm. Lower measurement 87 cm. Secondary hair growth sparse. Elbow joints showed 30–35° extension deficiency. Shoulder outline sloping (Fig. 1).

Repeated X-ray examinations revealed malformation of the nose and of the mandibula, with a mandibular angle of almost 180°. However, the sella was normal (Fig. 2).

Other skeletal malformations were also detected, such as deformed capitulum radii and short phalanges of some of the fingers. Aortography revealed dysplasia of the right kidney.

Gynecological findings

Uterine sound measurement was 5–6 cm (prior to the administration of oestrogens only 4 cm). On palpation, the ovaries appeared of normal size. Vagina: normal size.

Laboratory findings (The normal range is shown in parentheses.)

Serum analyses

sodium 141 mEq/l (136–142)
potassium 4.8 mEq/l (3.2–5.0)
calcium 4.5 mEq/l (4.5–5.5)
chloride 105 mEq/l (90–110)
creatinine 1.0 mg% (0.8–1.2)
blood sugar 105 mg% (60–100)
protein bound iodine 4.5 µg/100 ml (4.0–8.0)

The basal metabolic rate of the patient was −17%. A ^{131}I-test indicated normal values. She had a positive sex chromatin and the karyotype in blood culture was 46.

Hormone assays

"Total gonadotrophins" in urine: around 13 M.U. (normal values).

"Total" oestrogens (i.e. the sum of oestrone, 17β-oestradiol and oestriol): 10 µg/24 h (low value).

Urinary pregnanediol: 16 mg/24 h (strongly elevated value for an amenorrhoeic patient).

Urinary pregnanetriol: 5.0 mg/24 h (elevated value).

17α-Hydroxycorticosteroids: 25 mg dehydroepiandrosterone equiv./24 h ("high normal" value; normal range: 5.0–25.0 mg/24 h).

Total 17-ketosteroids: 7.0 mg dehydroepiandrosterone equiv./24 h (normal value).

Fractionated determination of 17-ketosteroids: The pattern is indicated in Fig. 3.

The androsterone and etiocholanolone fraction was 43.8% of the total, and 11-oxygenated steroids corresponded to 26.4% of the total, indicating normal

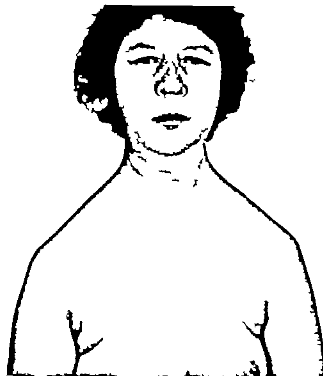


Fig 1 Sloping shoulder outline in the patient aged 33

rono, Rome, Italy The potency of this material was bioassayed in this laboratory (Diczfalusy et al., 1964). Each ampoule contained 85 I.U. of follicle stimulating hormone (FSH) and 55 I.U. of interstitial cell stimulating hormone (ICSH)

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Pregnenolone-7α-^{3}H (New England Nuclear Co., Boston, Mass., USA) Lot 51 287 22, with a specific activity of 7.3 mCi/mM, was purified by thin layer chromatography in the systems ethyl acetate/benzene (15 85) and benzene/ethanol (90 10), followed by partition chromatography on Celite, using n-hexane/70% aqueous methanol (v/v). Its radiochemical purity was established by repeated crystallisations.

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Evaluation of endometrial biopsy specimens. This was the same as that described in a previous communication (Diczfalusy et al., 1964).

Estimation of sex chromatin and karyotype by blood culture This was kindly carried out by Professor J Lindsten, Arhus, Denmark.

CASE REPORT

Anamnestic data

A thirty-three-year-old married woman, who is number among 6 sisters and brothers. Her sister is 30 years old and has 3 healthy children.

The first signs of puberty appeared at the age of 17–18 and consisted of a slight growth of the mammary glands and the appearance of some pubic and axillary hair. No menstrual bleedings or any further development of the secondary sex characteristics occurred until the age of 6, when oestrogen treatment resulted in moderate growth of the breast and menstrual-like bleeding.

At the age of 16 she was operated upon because of an appendicitis.

From the age of 18, she has experienced occasional abdominal pains accompanied by nausea. Because of this, she was hospitalized in another hospital. According to the available records of the gynecological examination: "No, or very small uterus, with walnut-sized resistance on its right side



Fig. 2. X-ray picture of the skull. Note the mandibular angle and the malformation of the nose.

At the age of 33, she married a man aged 28. She was admitted now to the hospital because of infertility.

Clinical findings

The patient displayed hypogonadic proportions with span of 172 cm and a height of 167 cm. Lower measurement 87 cm. Secondary hair growth sparse. Elbow joints showed a 30–35° extension deficiency. Shoulder outline sloping (Fig. 1).

Repeated X-ray examinations revealed malformation of the nose and of the mandibula, with a mandibular angle of almost 180°. However, the sella was normal (Fig. 2).

Other skeletal malformations were also detected, such as deformed capitulum radii and short phalanges of some of the fingers. Aortography revealed dysplasia of the right kidney.

Gynecological findings

Uterine sound measurement was 5–6 cm (prior to the administration of oestrogens only 4 cm). On palpation, the ovaries appeared of normal size. Vagina: normal size.

Laboratory findings (The normal range is shown in parentheses.)

Serum analyses

sodium 141 mEq/l (136–142)
potassium 4.8 mEq/l (3.2–5.0)
calcium 4.3 mEq/l (4.5–5.5)
chloride 105 mEq/l (90–110)
creatinine 1.0 mg% (0.8–1.2)
blood sugar 105 mg% (60–100)
protein bound iodine 4.5 µg/100 ml (4.0–8.0)

The basal metabolic rate of the patient was −17%. A ^{131}I-test indicated normal values. She had a positive sex chromatin and the karyotype in blood culture was 46

Hormone assays

"Total gonadotrophins" in urine: around 13 M.U. (normal values).

"Total" oestrogens (i.e. the sum of oestrone, 17β-oestradiol and oestriol): 10 µg/24 h (low value).

Urinary pregnanediol 16 mg/24 h (strongly elevated value for an amenorrhoeic patient).

Urinary pregnanetriol 5.0 mg/24 h (elevated value).

17α-Hydroxycorticosteroids: 23 mg dehydroepiandrosterone equiv./24 h ("high normal" value: normal range: 5.0–23.0 mg/24 h).

Total 17-ketosteroids: 7.0 mg dehydroepiandrosterone equiv./24 h (normal value).

Fractionated determination of 17-ketosteroids: The pattern is indicated in Fig. 3.

The androsterone and etiocholanolone fraction was 43.8% of the total, and 11-oxygenated steroids corresponded to 26.4% of the total, indicating a normal

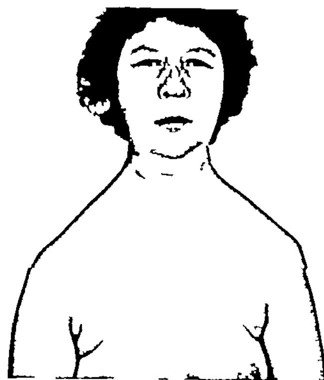


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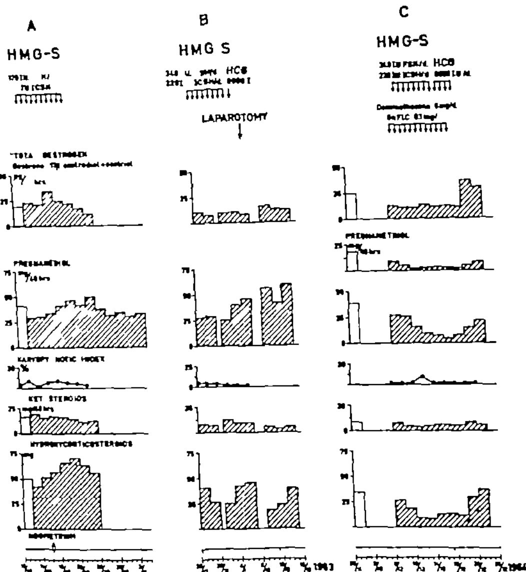


Fig. 4 Lack of urinary oestrogen and pregnanediol response to massive doses of human menopausal gonadotrophin (*HMG*) with or without human chorionic gonadotrophin (*HCG*). Open columns, pretreatment values. Endometrical biopsies invariably indicated an atrophic endometrium (*A*).

total of 12 days. It can be seen that this combined treatment resulted in significant depression of urinary pregnanediol and pregnanetriol excretion as well as in major decrease in 17-ketosteroids and 17α-hydroxycorticosteroids. There was no rise whatsoever in the urinary oestrogen excretion during adrenal suppression and gonadotrophin stimulation. However upon discontinuation of the adrenal suppression, a limited increase in urinary oestrogen excretion was observed. There was no sign of an increased oestrogen production as far as this could be judged on the basis of the vaginal cytology and endometrial biopsy.

Steroid metabolic studies

In order to explore the possible existence of systemic steroid metabolic blocks, a combination of tritium labelled pregnenolone (35.0 μc) and ¹⁴C-labelled androstenedione (3.3 μc) were ad-

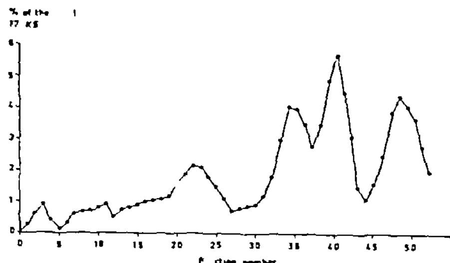


Fig. 3. Pattern of fractionated 17-ketosteroids found in the urine of the patient. Gradient elution chromatography on aluminum oxide. For the identity of the individual compounds present in the various peaks, consult text.

distribution (e.g. Böttiger & Lisboa, 1967). The etiocholanolone to androsterone ratio was 1.25 (normal values according to Böttiger & Lisboa (1967) 1.4 ± 0.36).

Aldosterone: 0.73 and 0.84 µg/48 h (low values).

Tetrahydrocortisol: 1.8 and 1.6 mg/48 h (normal values).

Tetrahydrocortisone: 3.7 and 4.. mg/48 h (normal values).

Tetrahydro-11-desoxy-cortisol: less than 0.5 mg/48 h (normal value).

Bioassay of urinary oestrogens: less than ..0 µg oestradiol equiv./ 4 h (low value).

Karyopyknotic index in vaginal smear: never exceeding 10 (low value).

Endometrial biopsies: Invariably atrophic, without signs of proliferation.

EXPERIMENTAL

On the basis of the hormone assays, the patient was suspected to have a primary amenorrhoea, presumably of hypothalamic origin. Therefore treatment with human gonadotrophins was initiated, as indicated in Fig. 4.

In the first course of treatment (indicated by *A* in Fig. 4) a daily dose of 170 I.U. of FSH (containing also 110 I.U. of ICSH) was given for 10 days. As indicated by the data of Fig. 4 this treatment did not result in any significant rise of urinary oestrogen excretion or of the karyopyknotic index. The endometrium remained atrophic. However, there seemed to be an increased elimination of pregnanediol and 17α-hydroxycorticosteroids in the urine, although the pretreatment excretion of these steroid groups was already pathologically elevated.

A new course of gonadotrophin treatment was given approximately one month later. As indicated by Fig. 4 *B* this time daily doses of as much as 340 I.U. of FSH (and 220 I.U. of ICSH) were given during 8 days, followed by a single injection of 6000 I.U. of HCG on the 9th day. Neither the urinary oestrogen excretion, nor the karyopyknotic index indicated any increased oestrogen formation. The biopsy revealed an atrophic endometrium. Explorative laparotomy was performed on the 10th day of this treatment course. The ovaries were found enlarged to a size approximately twice normal. In the right ovary a walnut sized cyst was found, which was filled with old clotted blood. However, several fresh corpora lutea were observed. The histological pictures indicated a normal tunica albuginea and a number of primordial follicles normal for the age (Fig. 5).

No secondary follicles were seen in the sections studied. However, several Graafian follicles were present both with and without signs of early atresia. Two or three fresh corpora lutea were also seen (Fig. 6) together with a few corpora albicantia.

The macroscopically observed cyst in the upper pole of the right ovary appeared to be a Graafian follicle with moderately luteinized granulosa, originating probably from the first course of treatment.

One year later, the gonadotrophin stimulation was repeated in connection with adrenal cortical suppression, as shown in Fig. 4 *C*. Again, 340 I.U. of FSH (and ..20 I.U. of ICSH) were given daily for 8 days. This treatment was followed by the administration of 6000 I.U. of HCG during 4 days. Dexamethasone (6 mg/day) and fluorhydrocortisone acetate (0.1 mg/day) were given simultaneously with the gonadotrophin course for a

Fig. 4. Lack of urinary oestrogen and pregnanediol response to massive doses of human menopausal gonadotrophin (*HMG*) with or without human chorionic gonadotrophin (*HCG*). Open columns: pretreatment values. Endometrial biopsies invariably indicated an atrophic endometrium (*A*).

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Fig. 5. Section of the r
ovary. Note the primor
follicle

ministered intramuscularly in 1.0 ml of arachis oil (April 3rd, 1965) and urine was collected during the subsequent 4 days. The elimination of radioactive material is indicated in Table I.

It appears from the data of Table I that elimination of tritium labelled material was m slower than that of the ^{14}C-labelled material. 4 days only 37.1 of the administered ^{3}H-

Fig. 6. Section of a fresh corpus luteum found in the right ovary.

Table I. *Urinary elimination of ^{3}H and ^{14}C-labelled material following the intramuscular administration of 35 μc of ^{3}H-labelled pregnenolone and 3.3 μc of ^{14}C labelled androstenedione*

The figures indicate percentage of the administered dose

Days	1	2	3	4	Total
^{3}H	17.9	9.7	6.4	3.1	37.1
^{14}C	62.3	8.5	4.6	2.5	77.8

belled material was eliminated, as compared to 77.8% of the ^{14}C-labelled steroids.

The urine excreted during the first 48 hours was combined. An aliquot of it was subjected to enzyme hydrolysis,[1] the liberated steroids were extracted by ethyl acetate and subjected to a Girard separation. The enzyme hydrolysis was completed by solvolysis, and the solvolysable material was also subjected to Girard separation. The enzymic hydrolysis liberated more than 97% of both the conjugated ^{3}H-labelled and ^{14}C-labelled material. The small amount of solvolysable radioactive material was not studied further. As much as 95% of the urinary ^{14}C-labelled material was present as ketonic material; only 15% of the ^{3}H-labelled material was ketonic. A small aliquot of the ketonic material was used for the determination of the ratio of etiocholanolone to androsterone (e.g. according to Böttiger & Lisboa, 1967). The ratio of these labelled compounds was 1.01. The rest of the ketonic fraction was subjected to column chromatography on alumina with gradient elution (as indicated in the example given in Fig. 1) and the fractions eluted were pooled in four groups (e.g. Böttiger & Lisboa, 1967) as follows: group I, fractions 1–15; group II, 16–29; group III, 30–42; and group IV, 43–50.

The material eluted in group I was not studied further. Using the material constituting group II, attempts have been made to isolate dehydroepiandrosterone, epiandrosterone and epietiocholanolone, using TLC with three developments in the system cyclohexane/ethyl acetate (40:60). The material corresponding to the mobility of these three steroids was eluted and crystallized with the corresponding carrier. All ^{3}H- and ^{14}C-labelled material was dissociated from the authentic carriers.

The material present in group III was subjected to TLC in the system cyclohexane/ethyl acetate (50:50) with three developments (e.g. Lisboa, 1969), and the eluted androsterone and etiocholanolone-like material was chromatographed again in TLC, using this time cyclohexane/ethyl acetate (40:60) with two developments. The labelled androstenedione and etiocholanolone were then crystallized to constant specific activity (Table II).

The material constituting group IV was chromatographed in TLC, using cyclohexane/ethyl acetate (50:50) with three developments. No ^{3}H-labelled material was detected and all ^{14}C-labelled material exhibited a mobility of 64 cm, corresponding to that of 11β-hydroxyetiocholanolone or 11-oxoandrosterone. Unfortunately the scarcity

[1] Enzyme hydrolysis was carried out by the use of a Helix pomatia preparation (Industrie Biologique Française, S.A., Gennevilliers, France), using 1000 units of β-glucuronidase and 500 units of sulphatase per ml urine (conditions: 0.1 M acetate buffer, pH 5.1, at 37° for 48 hours).

Table II. *Radiochemical homogeneity of ^{14}C-labelled androsterone and etiocholanolone isolated from the urine following the administration of ^{3}H-labelled pregnenolone and ^{14}C-labelled androstenedione*

No ^{3}H-labelled material was present in the crystalline material. Figures indicate disintegrations per minute per mg material

	Androsterone			Etiocholanolone	
Crystallizations[a]	C[b]	M. L.	Crystallizations[c]	C[b]	M.L.
Ethyl acetate	542	1115	Ethyl acetate	1434	1462
Benzene/n-hexane	519	600	Benzene/n-hexane	1398	1343
Acetone/n-hexane	561	569	Acetone/n-hexane	1389	1396
Benzene/n-hexane	520	580			
Acetone/n-hexane	550	586			

[a] Initial specific activity: 570 DPM/mg. [b] C: Crystals. M.L.: Mother liquors.
[c] Initial specific activity: 1178 DPM/mg.

Table III. *Radiochemical homogeneity of H-labelled pregnanediol and pregnanetriol isolated from the urbe following the administration of H-labelled pregnenolone and C-labelled androstenedione*

No [4]C labelled material was present in the isolated steroids

	Pregnanediol			Pregnanetriol	
Crystallisations	C[b]	M.L.	Crystallisations[d]	C[b]	M.L.
Methanol	2024	2442	Methanol	181	1213
Methanol	1835	1900	Benzene	124	644
Methanol/benzene	1797	1849	Methanol/benzene	102	182
Ethyl acetate/methanol	1874	1853	Methanol/petroleum ether	88	92
Methanol/petroleum ether	1786	1790	Ethyl acetate	91	101
Methanol/petroleum ether	1828	1789			

Specific activity 1994 DPM/mg. [b] C = Crystals. M. L. = Mother liquors. [d] *Specific activity 1460 DPM/mg.*

of the radioactive material in this fraction precluded crystallization.

The *non-ketonic fraction* was subjected to absorption chromatography on alumina and was eluted with 0.8% (group A), 3.0% (group B) and 6.0% (group C) ethanol in benzene. In the material constituting group A, attempts were made to demonstrate the presence of 5α-pregnane-3β,20β-diol and 5α-pregnane-3β,20α-diol by crystallizing aliquots with authentic carriers. All radioactive material was dissociated from the two carriers during crystallisations. The material present in group B was subjected to TLC in system cyclohexane/ethyl acetate (50:50) with three developments, the eluted pregnanediol like material was chromatographed in TLC in system chloroform/ethanol (90:10) and crystallized (Table III).

The material corresponding to group C was subjected to TLC in system cyclohexane/ethyl acetate (50:50) with two developments, and then to another one in chloroform/ethanol (90:10) with three developments. The pregnanetriol-like radioactive material was then crystallized (Table III).

Another aliquot of the urine which was excreted during the first 48 hours was hydrolysed by boiling at pH 7.0 under ethyl acetate cover (e.g. Fotherby 1959) and the liberated material was extracted by ethyl acetate. Only 1–2% of the urinary conjugated radioactive material became liberated by this procedure. The urine was then subjected to hot acid hydrolysis according to the method of Brown (1955) and the liberated material was extracted by ether. Following the removal of the acidic material, the radioactive material was subjected to a phenolic partition between toluene and 1 n NaOH. The phenolic fraction thus obtained contained so little radioactive material that no further identification of its constituents could be carried out.

DISCUSSION

The analysis of the urinary steroid metabolites in this patient revealed several anomalies of steroid metabolism such as a strongly elevated excretion of pregnanediol and pregnanetriol as well as pathologically low aldosterone excretion. These changes were associated with certain signs of a diminished, or perhaps absent, oestrogen synthesis, such as a low karyopyknotic index in the vaginal smear and an atrophic endometrium. Although oestrogens (estimated in the form of Kober chromogens as well as by a semiquantitative bioassay) were not completely absent from the urine, the excretion values were low, approximately as low as in postmenopausal women. These low oestrogen values were associated with apparently normal total gonadotrophin values.

When as much as a total dose of 1700 I.U. of FSH was administered to her during a period of 10 days, no signs of an increased oestrogen production were seen. This dose is much higher than that generally used by us for the induction of ovulation in amenorrhoeic women (e.g. Diczfalusy et al. 1964, Johannisson et al., 1965). Since it is established that the individual sensitivity of patients to human pituitary or menopausal gonadotrophins may show marked differences (e.g. Crooke et al. 1966), in the next course we have doubled the dose of FSH and administered as much as daily doses of 340 I U. of FSH for 8 days, followed by a single dose of 6000 I.U. of HCG. Not even this stimulation gave rise to any

increased oestrogen production, as evidenced by the urinary oestrogen excretion, vaginal cytology and endometrial biopsy However at laparotomy several Graafian follicles and several fresh corpora lutea were found, indicating, that in the absence of any increased oestrogen secretion, follicle maturation and ovulation had taken place. An ovarian morphology as that observed in this patient is usually accompanied by the urinary excretion of almost milligram amounts of oestrogens (e.g. Gemzell et al., 1958 Diczfalusy et al., 1964 Johannisson et al., 1965).

In an attempt to exclude the possibility that the increased secretion of adrenocortical steroids interfered with the ovarian steroidogenic response, the adrenal cortical activity was suppressed by dexamethasone during gonadotrophic stimulation. Although the urinary excretion of pregnanediol and pregnanetriol was greatly depressed, no evidence of an increased oestrogen secretion could be obtained during HMG stimulation. It appears therefore that little, if any oestrogen was secreted by the maturing follicles and fresh corpora lutea. The marked rise in urinary Kober chromogens, which was observed upon discontinuation of adrenal suppression, might suggest the secretion of an adrenal β-unsaturated 3-ketonic steroid which might be subsequently aromatized by the liver

To find out the possible existence of steroidogenic blocks, mixture of ^{3}H-labelled pregnenolone and ^{14}C-labelled androstenedione was administered to the patient, and some of the principal metabolites were isolated from the urine in radiochemically homogeneous form. The urinary elimination of the ^{3}H-labelled material was much less than that of the ^{14}C-labelled material during the first 4 days of experiment, suggesting that the metabolites formed from pregnenolone are either retained in the organism for a much longer period, or are eliminated mainly by the faecal route. Our low recovery of ^{3}H-labelled metabolites from the urine is in agreement with the data published following the administration of 17α-hydroxypregnenolone (e.g. Roberts et al 1961 Romanoff et al., 1963)

The isolation studies revealed that the administered ^{3}H-labelled pregnenolone was converted to pregnanediol and some pregnanetriol. However the isolated dehydroepiandrosterone, androsterone or etiocholanolone did not contain any ^{3}H-label. Furthermore, the conversion of the administered pregnenolone to epiandrosterone or epietiocholanolone could also be excluded. The amount of phenolic material recovered indicated that little, if any aromatic steroid was formed. The ^{14}C-labelled precursor administered (androstenedione) was converted to androsterone and etiocholanolone and in normal proportions. No 3β-epimeric reduction products or phenolic metabolites were detected.

These data seem to suggest a defect in the side-chain splitting and aromatizing enzyme systems. In vitro studies indicate that human ovarian tissue is able to hydroxylate pregnenolone to 17-hydroxypregnenolone, remove the side-chain of this steroid (MacAuly & Weliky 1968) and aromatize the C 19 steroid formed (Axelrod & Goldzieher 1962 Ryan & Smith, 1961). In vivo experiments in which 17α-hydroxypregnenolone was administered to volunteers indicate that part of the administered steroid was converted to dehydroepiandrosterone, androsterone and etiocholanolone (Roberts et al., 1961 Solomon et al., 1960 Fukushima et al., 1963) It is also established that a part of androstenedione administered to volunteers is converted to oestrogens (MacDonald et al., 1967).

Reports in the literature on a deficient ovarian aromatizing enzyme system are scanty However Axelrod & Goldzieher (1962) reported a case of polycystic ovarian disease, with the apparent lack of aromatizing ability It could not be established in our present case, whether the lack of oestrogen formation was due to a deficient aromatizing, side-chain splitting, or 3β-dehydrogenating enzyme system, or to combination of several of these deficiencies. Because of lack of further co-operation of the patient, it was not possible to carry out additional metabolic studies.

At any rate, our data indicate that follicle maturation and corpus luteum formation may take place without a concommittant synthesis of oestrogens. Whether the eggs developing in such follicles are fertilizable, remains to be established.

ACKNOWLEDGEMENTS

The expenses of this investigation are defrayed by Research Grants from the Ford Foundation and from the Swedish Medical Research Council. We are indebted to Professor B Hökfelt for the estimation of aldosterone and of certain reduced corticosteroid metabolites, and to Professor J Lindsten for the sex chromatin and karyotype determination.

REFERENCES

Allen, W M J Clin Endocr *10* 71 1950.

Allen, E. & Doisy E. J Am Med Assoc *81* 819 1923

Appleby J L, Gibson, G Norymberski, J K. & Stubbs, R. D Biochem J *60* 435 1955

Axelrod, L. R. & Goldzieher J W J Clin Endocr *22* 431 1962.

Birke, G Diczfalusy E. & Plantin, L.-O J Clin Endocr *18* 736, 1958.

Brown, J B. Biochem J *60* 185 1955

Brown, J B., Bulbrook, R. D & Greenwood, F C., J Endocr *16* 49 1957

Böttiger L. E. & Lisboa, B. P., Z Klin Chem u. Klin. Biochem *5* 176, 1967

Crooke, A. C., Butt, W R. & Bertrand, P V Acta Endocr (Kbh), Suppl. 111 1966.

Diczfalusy E., Johannisson, E., Tillinger K.-G & Bettendorf, G Acta Endocr (Kbh), Suppl. 90 35 1964

Diczfalusy E. & Westman, A.. Acta Endocr (Kbh) *1* 3 1 1956.

Fotherby K., Biochem J *73* 339 1959

Fukushima, D K., Bradlow H. L., Hellman, L. & Gallagher, T F., J Clin Endocr *23* 66, 1963

Gemzell, C. A., Diczfalusy E. & Tillinger K.-G J Clin Endocr Metab *18* 1333 1958

Gemzell, C. A., Diczfalusy E. & Tillinger K.-G Acta Obstet Gynec Scand *38* 465 1959

Goebelsmann, U Sjöberg, K., Wiqvist, N. & Diczfalusy E. Acta Endocr (Kbh) *50* 261, 1965

Gustafsson, J A. & Lisboa, B. P Steroids *11* 555 1968

Hall, K. & Hokfelt, B.. Acta Endocr (Kbh) *52* 535 1966.

Hökfelt, B. & Luft, R.. Acta Endocr (Kbh) *32* 177 1959

Johannisson, E., Gemzell, C. A. & Diczfalusy E.. J Clin Endocr Metab *21* 1068, 1961

Johannisson, E., Tillinger K.-G. & Diczfalusy E.. Fert Steril *16* 292, 1965

Johnsen, S.. Acta Endocr (Kbh) *28* 69 1958

Klopper A. L, Michie, E. A. & Brown, J B J Endocr *12* 209 1955

Lisboa, B P Thin layer Chromatography of Steroids, Sterols and related compounds. In Steroids and Terpenoids, R. B. Clayton Ed, Methods in Enzymology vol. XV 3 Edts in Chief S. P Colowick and N. O Kaplan, Academic Press, New York, 1969

Loraine J A. Clinical Application of Hormone Assay Livingstone, Edinburgh, 1958.

McAulay M. A. & Weliky I J Clin Endocr Metab *28* 819 1968.

MacDonald, P C., Rembaut, R. P & Siiteri, P K.. J Clin Endocr Metab *27* 1103 1967

Mancuso, S., Dell'Acqua, S., Eriksson, G., Wiqvist, N & Diczfalusy E.. Steroids *5* 183, 1965

Plantin, L.-O. & Birke, G.. Acta Med Scand, Suppl. 291 1954

Roberts, K. D Vande Wiele, R. L. & Lieberman, S.. J Clin Endocr Metab *21* 1522, 1961

Romanoff, L. P Malhotra, K. K., Baxter M. N Thomas, A. W & Pincus, G J Clin Endocr Metab *28* 836, 1968

Ryan, K. J & Smith, O W J Biol Chem *236* 710 1961

Solomon, S., Carter A. C. & Lieberman, S J Biol Chem *235* 351 1960.

Stern, M.. J Endocr *16*, 180, 1957

Vestergaard, P., Acta Endocr (Kbh) *8* 193 1951.

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ORNITHINE-8-VASOPRESSIN A NEW VASOCONSTRICTOR USED FOR HAEMOSTASIS DURING OPERATION FOR GENITAL PROLAPSE

Ole Vagn Nielsen and Niels Valentin

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Abstract A new haemostatic agent POR-8, synthetic derivative of vasopressin, has been investigated under double blind trial conditions. It was found to be an effective haemostatic, significantly better than noradrenalin. Fully satisfactory haemostasis was obtained after local infusion of POR-8 in such low concentration as 0 05 IU/ml. The risk of cardiac arrhythmias when POR-8 is used with halothane appears to be minimal.

A minimum of bleeding and resultant clearer view of the operative field is clearly desirable in every operation, but particularly so when many small bleeding points would otherwise complicate the operative procedure unduly. Such a situation occurs (not exclusively) at vaginal operations for genital prolapse.

A combination of general anaesthesia and local infiltration of the operative field with noradrenalin or adrenalin is common and has been used for many years. But the procedure is not without risk. There are many reports of the occurrence of cardiac arrhythmias (particularly ventricular) when catecholamines have been used during halothane anaesthesia (Brindle et al., 1957 Hall & Norris, 1958, Katz et al., 1962 Millar et al., 1958 Johnstone & Nisbeth, 1961 Rosen & Roe, 1963). Arrhythmias also occur when cyclopropane or trichlorethylene is the general anaesthetic agent.

In recent years synthetic derivative of vasopressin, phenyl-lysin-vasopressin (Octapressin®) has come into use. There are many reports both of its haemostatic properties and of its use with halothane. (Dillon et al., 1958 Hochuli, 1962, Hochuli & Käser 1962, Missura & Weder, 1962, Klingenström & Westermark, 1964 Münchow & Denson, 1964 Rawstron et al., 1964 Shanks, 1964 Fisher et al., 1965 Orengo, 1965 Rintala, 1965 Rintala & Tammisto, 1965 *a* and *b* Aronsen & Nylander 1966 Kullander & Wide, 1966 Dahl, 1968). All agree that it is an effective haemostatic agent, though not so powerful as noradrenalin or adrenalin. However Hochuli (1962) Shanks (1964) and Dahl (1968) have reported the occurrence of cardiac arrhythmias when it is used with halothane

The persistence of this undesirable side effect of currently available vasoconstrictors makes the introduction of a new vasoconstrictor of considerable surgical and anaesthetic interest.

POR-8 (ornithine-8-vasopressin) is a synthetic derivative of vasopressin. By comparison with the *natural hormone, it has enhanced pressor action* and reduced anti-diuretic effect.

Some investigations of the haemostatic properties have already been made: Rintala (in press) in cleft palate surgery: Klingenström et al. (1966) compared the vasoconstrictor action of three hormones, octapressin, POR-8 and desaminooxytocin, with that of adrenalin. The following articles on the use of POR-8 are being printed. Burghardt, Wedge resection of the cervix, Diemath, Neurosurgery: Fankhauser Obstetric and gynaecological surgery: Hibler Tonsillectomy: Urbatura, Obstetric and gynaecological surgery: and Zeller A series of operations, mainly oto-rhino-laryngological. In some of these cases compatibility with general anaesthetics was also investigated.

AUTHORS' INVESTIGATIONS

Our investigations were conducted at St. Elisabeth Hospital, Copenhagen between September 1966 and February 1967. The haemostatic action of POR-8 was tested during series of operations for genital prolapse.

Table I

Age (y)	Age-distribution Group I	Group II	Group III	Group IV	Total
20–29	1	1			2
30–39	3	1			4
40–49	1	4	7	4	16
50–59	10	11	11	3	35
60–69	7	7	6	2	22
70–79				7	7
80–				2	2
Total	22	24	24	18	88

Table II

	No of patients	Type of operation Ant. vaginal repair	Post. vaginal repair	Amputation of the cervix
Group I	22	22	10	6
Group II	24	24	6	9
Group III	24	23	8	11
Group IV	18	16	8	9

The investigation was conducted as a double blind trial using POR-8 noradrenalin and a placebo.

70 patients under 70 years of age were involved. All patients with more than the mildest degree of pulmonary or cardiovascular disease were excluded. For instance *diastolic BP > 100 mm Hg* warranted exclusion.

Patients were allotted t random to one of three groups:

Group I. received noradrenalin 1 200,000,
Group II. received placebo,
Group III. received POR-8 0.1 IU ml.

To these basic groups, we added a *fourth* composed of patients over 70 years of age patients with cardiac disease who had been excluded from the first three groups, and six young otherwise healthy patients added to make the group of comparable size with groups I–III (in all 18 patients)

Group IV received POR-8, 0.05 IU/ml.

The age range is shown in Table I. It may be seen that the average age is very similar in Groups I III, but higher in group IV

General anaesthesia used for all patients was halothane (WHO) 0.5–1 0% N_2O and O_2 (usually 7+2 l/min) administered in a non-rebreathing system (Ruben or Ambu-E valve). Respiration was controlled. Pulse, BP and E.C.G were monitored throughout perations.

The basic operation performed was anterior and/or posterior repair with or without amputation of the cervix. Table II shows the incidence of each operative procedure in the four groups.

The operative field was infiltrated with the unknown preparation averaging 17 ml/patient.

Apart from the infiltration no other haemostatic procedures, ligatures or undersewing, were used, except hen the cervix was amputated, when the uterine eels at the utero-cervical junction were ligated.

88% of the operations were performed by only two surgeons (66% + 22%). Average duration of operation—about 35 min—varied little in any of the groups.

All blood lost during operation and during the first 24 hours postoperatively was collected and weighed.

The *results have been statistically evaluated and pre*sented using analysis of variance (Hald, 1948), based on a programme worked out by K. E. Keber Nielsen, a civil engineer

The work was done at "The Northern Europe University Computing Centre (NEUCC) on an IBM 7090 computer

Statistical data

If observations are designated $x_1 \; x_2 \; \ldots \; x_N$,

N = number of observations

$m = 1/N \sum_{i=1}^{N} x_i$, the mean value of observations

$S^2 = 1/(N-1) \sum_{i=1}^{N} (x_i - m)^2$ the variance of observations

$S = \sqrt{S^2}$ the standard-deviation of observations

S = common estimate on the standard-deviation in all groups

F = the quotient of variance ("Fischer s F")

RESULTS

Since the distribution of specific operations in the different groups (I–IV) is the same, the collected results are based on the average value determined for each group.

In the course of the operations, the surgeons gave opinion of the effectiveness of the haemostasis, grading it—good or bad. Table III shows clearly that the best haemostasis (subjectively evaluated) was obtained in groups III and IV Surgeons were unaware of the nature of the infiltration *in group* III patients, but knew that group IV patients were being infiltrated with POR-8, 0 05 IU/ml.

Table III

	No. of *patients*	Haemostasis *Good*	Bad
Group I	19	9	10
Group II	24	12	12
Group III	24	20	4
Group IV	18	16	2

$F = 4.99$ ($p < 0.01$) with 3 and 83 degrees of freedom.

There is significant statistical difference between the four groups ($F = 4.99$ $p \leq 0.01$)

Actual haemostasis, as reflected in measurement of blood loss during operation is shown in Table IV Again haemostasis was clearly most effective in group III ($m = 48.33$ g) and group IV ($m = 40.56$ g) The loss in these groups was virtually half of that in the noradrenalin and placebo groups. Analysis of variance further confirms the results. significant difference between groups: $F = 4.67$ $p \leq 0.01$

Postoperative bleeding in the first 24 hours was small—between 25 g and 40 g, least in group IV There was no clear significant difference between the groups (Table V).

DISCUSSION

All the previously noted authorities whose work is in print (Burghardt, Diemath, Fankhauser Hibler Zeller) conclude that POR-8 is an effective haemostatic, but their conclusions are largely subjective.

Our evaluated results add statistical confirmation to their impressions that POR-8 is an extremely *effective* haemostatic agent, significantly better than noradrenalin. Blood loss during operation for genital prolapse was approximately halved fter POR-8 infiltration compared with loss after noradrenalin or placebo infiltration.

Table IV shows that POR-8 in concentration of only 0.05 IU/ml (group IV) gives good haemostasis. Possibly even a lesser concentration will give as good results. The experimental studies of Klingenström et al. (1966) indicate that between 0.005 and 0.001 IU/ml may be adequate (particularly for skin transplants).

Where the word "significant" appears in the text, it is used in the statistical sense.

Table IV

	No of patients	Blood-loss during operation measured in g		
		m		
Group I	22	83.43	78.80	
Group II	24	98.96	74.30	
Group III	24	48.33	35.34	60.38
Group IV	18	40.56	33.25	

$F = 4.67$ ($p \leq 0.01$) with 3 and 83 degrees of freedom.

Table V

	No. of patients	Postop. blood-loss (g)		
		m		
Group I	22	39.55	24.25	
Group II	24	33.13	19.33	20.66
Group III	24	38.13	23.21	
Group IV	18	25.83	12.16	

$F = 0.177$ ($p > 0.05$) with 3 and 83 degrees of freedom.

There was no marked postoperative bleeding when the POR-8 effect had worn off. What little bleeding there was, was similar in all groups. It is noteworthy that the influence on the circulation, manifest by changes in BP and pulse rate, was very modest in all groups (in groups III and IV zero)

There was a cardiac arrhythmia noted (isolated extra-systoles) in only one patient, and it should be remembered that such an arrhythmia has been reported during halothane anaesthesia even when catecholamines have not been used (Black et al., 1959 Johnstone & Nisbeth, 1961 Katz et al., 1962, Millar et al., 1958).

None of the authors whose work is in press (Burghardt, Diemath, Fankhauser Hibler Rintala, Zeller) has observed any arrhythmias when POR-8 was used along with local anaesthesia, nor when it was used during general anaesthesia (in number of cases with halothane) This point is discussed in detail elsewhere (Valentin & Nielsen, 1969).

CONCLUSIONS

A double blind trial has shown that POR 8 is a very effective haemostatic agent, significantly better than noradrenalin. The risk of producing cardiac arrhythmias when POR-8 is used during halothane anaesthesia seems to be very small. However further investigations should probably be made before using POR-8 when patients have marked coronary insufficiency

In concentration of only 0.05 IU/ml (and probably in weaker solution) POR-8 gives completely satisfactory haemostasis during operations for genital prolapse. The operative procedure is facilitated by the clear view afforded of the field. Blood loss is minimal even when the total Manchester operation (anterior and posterior repair and amputation of the cervix) is performed.

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REFERENCES

Aronsen, K. F & Nylander G Acta Chir Scand *131* 443 1966.

Black, G. W Linde H. W Dripps, R. D & Price H. L. Brit J Anaesth *31* 238, 1959

Brindle C. F Gilbert, R. G. B. & Millar R. A. Canad Anaesth Soc J *4* 65 1957

Burghardt, E. In press.

Dahl, A. Nord Med 79 119 1968.

Diemath, H In press.

Dillon, T F Marbury B. E., Bonsnes, R. W Douglas R. G & du Vigneaud, V Obst and Gynec *11* 363 1958

F olkhauser B In press.

Fisher S J Gehrig, J & Green, H. J Amer Dent Ass *70* 1189 1965

Hald, A. Statistiske Metoder København, 1948.

Hall, K. D & Norris, F H., Jr Anesthesiology *19* 631, 1958.

Hibler N In press.

Hochuli, E. Schweiz Med Wschr 9 654 1962.

Hochuli, E & Käser O Triangel *8* 363 196.

Johnstone M. & Nisbeth, H. J A. Brit J Anaesth *33* 9 1961

Katz, R. L., Matteo, R. S. & Papper E M. Anesthesiology *3* 597 1962.

Klingenström, P & Westermark, L. Acta Anaesth Scand *8* 61 1964

Klingenström, P Nylén, B. & Westermark, L. Acta Anaesth Scand, Suppl. 23 366, 1966.

Kullander S. & Wide E. Acta Obst Gynec Scand *45* 102, 1966.

Millar R. A., Gilbert, R. G B & Brindle G F Anaesthesia *13* 164 1958

Mismura, T & Weder A. Pract Oto-Rhino-Laryng *24* 49 1962.

Munchow O B. & Denson, J S. Surgery *56* 989 1964.

Orengo, F Gynaecologia *160* 1, 1965

Rawstron, R. E., Hutchinson, B. R. & McNeill, T D M. NZ Med J *63* 297 1964

Rintala, A. In press.

Rintala, A. Act Chir Scand *129* 288, 1965

Rintala, A. & Tammisto, T Ann Chir Gynec Fenn *54* 52, 1965 *a*.

Rintala, A. & Tammisto, T Der Anaesthetist *14* 181, 1965 *b*.

Rosen, M. & Roe R. B. Brit J Anaesth *35* 51, 1963

Shanks, C. A. NZ Med J *63* 664 1964

Urbatus, W Praxis *56* 1755 1967

Valentin, N & Nielsen, O V Acta anaesth Scandinav *13* 63 1969

Zeller K. In press.

Acta Obstet Gynec Scand 49: 49–55 1970

STAGE AND PROGNOSIS OF OVARIAN CYSTADENOCARCINOMAS

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Abstract. A series of 289 patients with primary ovarian cystadenocarcinomas is presented. Of the tumours, 183 were of the serous and 106 of the pseudomucinous type. The total number includes 41 borderline serous and 18 borderline pseudomucinous cystadenocarcinomas. In this series the survival rates were the same in pseudomucinous and serous cystadenocarcinomas. From the standpoint of survival rates there seemed to be no difference between bilateral and unilateral cases of stage I. No statistically significant difference was observed either with regard to the survival rates in cases of adherent and non-adherent tumours of stage I, although there seemed to be a tendency towards more favourable results for the non-adherent carcinomas. On evaluating the results from the standpoint of treatment, irradiation seemed to be of no use in cases in which the tumour was limited to the ovaries. The benefit of radiotherapy is questionable also in those cases where it is sure that the entire tumour has been successfully removed. On the other hand, in cases of widespread carcinoma the value of radiotherapy seems to be indisputable.

In the majority of clinical studies, ovarian carcinomas have been treated as one group under the same heading. Taylor (Munnell & Taylor 1949, discussion), however, pointed out that ovarian carcinoma is a group of diseases rather than a uniform disease, and that it is more useful to treat the various histogenetic types separately than to discuss the heterogenous group of ovarian carcinomas as a whole. In accordance with this view we have undertaken a study of cystadenocarcinomas, the largest and clinically most important group of ovarian carcinomas. Two histogenetic main types have been distinguished: serous and pseudomucinous tumours. Endometroid carcinoma is not treated separately in this paper. The prognosis of this latter type has been studied by Santesson & Kottmeier (1968) and Lauren et al. (1968).

Besides the histogenetic type of the tumour the clinical stage of extension and the histological degree of malignancy are the most important factors from the standpoint of prognosis. The purpose of this study was to estimate the prognosis of ovarian cystadenocarcinomas precisely on the basis of the clinical stage of extension, attention being paid also to the treatment. With regard to the degree of malignancy we have only distinguished between borderline tumours and true carcinomas. One of us (Purola, 1963) has previously graded part of the present material (110 serous cystadenocarcinomas from the period 1945–1956) and found that the prognosis was definitely better in patients with well-differentiated tumours than in those with tumours of a less mature type.

The classification of ovarian carcinomas into groups representing different clinical stages of extension offers considerable problems. The principles of classification applied in the previous literature deviate appreciably from each other. Some authors have distinguished different groups on the basis of the anatomical extension of the tumour at the time of operation, while others have used operability as a basis of classification. In certain papers both principles in conjunction have been applied. Cralon's (1938) classification, based on operability, may be cited as a typical example: Stage I, tumour totally operable; Stage II, tumour partially operable; Stage III, tumour inoperable. Hofman (1962) and van Orden et al. (1966) have reviewed the papers so far published in which staging of ovarian carcinomas has been attempted.

In the present study the clinical stages of extension were distinguished as recommended by the Cancer Committee of the International Federation of Gynaecology and Obstetrics. The F.I.G.O. groups are as follows:

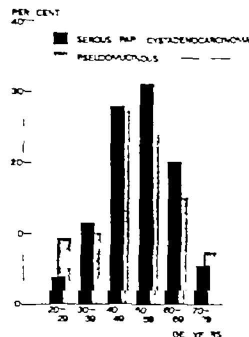


Fig 1 Age grouping of 183 serous and 106 pseudomucinous cystadenocarcinomas.

Stage I Growth limited to the ovaries.

I *a* Growth limited to one ovary no ascites.

I *b* Growth limited to both ovaries, no ascites.

I *c*. Growth limited to one or both ovaries ascites present with malignant cells in the fluid.

Stage II. Growth involving one or both ovaries with pelvic extension

II *a*. Extension and metastases to the uterus and tubes only

II *b* Extension to other pelvic tissues.

Stage III. Growth involving one or both ovaries with widespread intraperitoneal metastases to the abdomen (the omentum, the small intestine and its mesentery)

Stage IV Growth involving one or both ovaries with distant metastases outside the peritoneal cavity

Special category Unexplored cases which are thought to be ovarian carcinoma (surgery explorative or therapeutic, not having been performed)

Note The presence of ascites does not influence the staging *for stages II, III and IV*

Since the ascitic fluid, if present, as a rule had not been histologically investigated, stage I *c* had to be disregarded. Moreover since the series consists of surgically treated cases, and patients with distant metastases are seldom operated upon, the number of cases of stage IV is small, and the special category is not represented at all.

MATERIAL

The series consists of 289 patients with ovarian cystadenocarcinomas, treated in Departments I and II of Gynaecology and Obstetrics, Helsinki University Central Hospital, during the period 1945–1960. *Of the tumours*, 183 were serous and 106 pseudomucinous. Mixed forms were classified according to the dominant type of malignancy. The above mentioned figures include 59 borderline cases, 41 of which were classified as serous and 18 as pseudomucinous. During the period under review a total of *620 patients with malignant ovarian tumours were treated* in our hospital. The cystadenocarcinomas constitute 46.6% of all ovarian primary malignancies. In all of the present 289 cases laparotomy was performed, and specimens for histopathological investigation were obtained. All specimens were investigated by the same pathologist (Professor C. von Numers M.D.). The age distribution of the series is shown in Fig. 1

Management During a period as long as that covered by the present study methods of treatment always change to some extent. However throughout this time the same main principle was applied: as radical surgery as possible, followed by radiotherapy Since the use of cytotoxic drugs was not adopted in our hospital until 1959 such therapy as an adjunct to surgical treatment was given in only 20 of the present cases.

The operations most frequently performed was total or subtotal hysterectomy with removal of both adnexa ("radical surgery") 179 cases. Excision of the tumour alone ("conservative surgery") was performed in 83 cases. In 27 cases only exploratory laparotomy could be performed.

In the majority of the present cases, postoperative X-ray therapy was given using fixed fields or pendulum therapy A total of 14 patients received *irradiation*. In some cases the treatment was given preoperatively the purpose being, as a rule to render a widespread tumour operable. In 46 cases vaginal radium treatment was given either pre- or postoperatively and in 27 cases intra-abdominal treatment with radioactive gold (Au[198]) was administered.

RESULTS

The distribution of the tumours by clinical stage of extension and the survival rates are shown in Table I When the whole series is considered, borderline tumours included, 167 patients (58%) belong to the group with stage I.

The serous type of carcinoma is more frequent in this group (92 cases) than the pseudomucinous *type (75 cases) The patients with carcinoma of*

Table I. *Stage and survival rates for 183 serous and 106 pseudomucinous cystadenocarcinomas*

Stage	Serous cystadenocarcinomas				Pseudomucinous cystadeno-carcinomas				Both together			
			Alive after five years				Alive after five years				Alive after five years	
	No	%	No.	%	No	%	No	%	No.	%	No.	%
Stage Ia	58		46	79	67		51	74	125		97	78
Stage Ib	34		29	85	6		4	50	42		33	79
Stage I	92	50	75	82	73	71	55	75	167	58	130	78
Stage IIa	3		3	100	5		1	20	8		4	
Stage IIb	22		13	59	8		3	38	30		16	
Stage II	25	14	16	64	13	12	4	31	38	13	20	53
Stage III	63	34	14	22	18	17	2	11	81	28	16	20
Stage IV	3	2	—	0	—	—	—	—	3	1	—	0
Total	183	100	105	57.3	106	100	61	57.5	289	100	166	57.4

stage III are twice as numerous as those treated for carcinoma of stage II (28% and 13% respectively).

Of the whole series, 166 patients (57.4%) were alive after five years. Fig. 2 shows the survival curves for the two types of cystadenocarcinoma separately and united. Although the curves seem to indicate that the survival time of patients with pseudomucinous carcinoma is shorter the difference between the *five year survival rates is* not statistically significant. It appears, moreover from the curves that mortality is highest within the first two years in both the serous and the pseudomucinous group. After this, the survival curves drop more slowly.

The involvement of both ovaries was recorded only in stage I, i.e. in 37% of the serous and 11% of the pseudomucinous cases. With regard to prognosis, no statistically significant difference was found between the unilateral and bilateral cases.

In 167 cases of stage I the tumour was adherent to the surrounding tissues. Of these patients 41 (72%) were alive after five years. Among those 110 patients whose tumours were not adherent, the corresponding figures were 89 and 81%. The difference is not statistically significant, but it may be regarded as expressing tendency.

The distribution of the borderline tumours by clinical stage of extension and their survival rates appear in Table II. It may be seen that, of 41 patients with tumours of the serous type only one died within five years, the five-year survival rate being 98%. The prognosis of the pseudomucinous

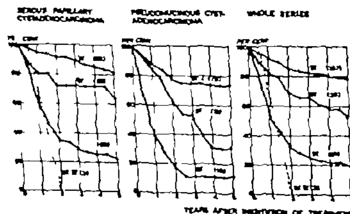


Fig. 2. Absolute five-year survival curves for serous and pseudomucinous cystadenocarcinomas according to clinical stage of tumour.



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ment, patients were more often in stage III than in stage II. This seems to indicate that when carcinoma begins to spread outside the ovaries, it very rapidly extends into the pelvis and further into the abdominal cavity. The same appears from a study recently published by Munnell (1968). On the basis of the present series it would seem that serous cystadenocarcinoma spreads more rapidly into the abdomen than the pseudomucinous type. Allan & Hertig (1949), however, arrived at a contrary result.

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When the both types of carcinoma were considered separately and jointly mortality was found to be highest within the first two years. This is consistent with the report of Munnell & Taylor (1949) according to which 60% of the deaths occurred within the first one and a half years, after which the survival dropped more slowly in all types of carcinoma.

The prognosis of serous borderline tumours proved to be very favourable: of 41 patients with tumours of this type, 40 were alive after five years. This corroborates the results in previous investigations (Purola, 1963. Lauren et al., 1968). On the other hand, the prognosis of pseudomucinous borderline tumours seemed to be somewhat poorer.

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Stage I	35	34	17	13
Stage II*a*	1	1	—	—
Stage IIb	-	-	—	—
Stage II	3	3	—	—
Stage III	3	3	1	1
Stage IV	—	—	—	—
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borderline tumours was poorer 4 patients out of 18 died within five years, the five year survival rate being 78 %

As mentioned previously subtotal hysterectomy with removal of both adnexa ("radical surgery") and supplementary radiotherapy was the method of treatment most frequently used in the present series. It was carried out in 139 cases (Table III) The five-year survival rate in this group is 59 Radical surgery alone was performed on 40 patients, 31 of whom (78) survived five years. On comparing the group with stage I tumours treated by radical surgery plus radiotherapy and the group treated by radical surgery alone it is striking that the five-year survival rate is 74 in the former and 9_ in the latter

It appears, in addition, from Table III that the five-year survival rate in the group of 59 patients treated by conservative surgery plus radiotherapy is 54 while the corresponding figure for the group treated by conservative surgery alone is 78 If only cases in stage I are considered, the five year survival rate is 72 % for the patients who received the combined treatment, while of those treated by conservative surgery alone, 84 survived five years.

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Conservative surgery	I	23	84
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basis of a later series, Munnell (1968) states that irradiation is required when a carcinoma has extended outside the ovaries and in these cases of stages I and II in which the histological structure of the tumour shows a low degree of differentiation. In the present series, surgical treatment alone seemed to yield better results than surgery plus irradiation (Table III) This obtains to both radical and conservative surgery The result was the same when the comparison was performed by stages, i.e. by comparing all stages together and by distinguishing stage I It should be borne in mind, however that the same stage includes a number of more "favourable" cases, in which radiotherapy is more likely to be abandoned. In other words, the group of patients treated by surgery alone includes a relatively greater number of "favourable" cases, which may influence the end result.

Opinions differ concerning the justification for postoperative radiotherapy but the majority of authors regard this as an indispensable adjunct to surgical treatment. Some investigators, however consider the value of irradiation as open to question (Saxén et al., 1963). Latour & Davis (1957) were even able to show that the results in groups treated both surgically and by irradiation were poorer than the results obtained by surgical treatment alone. The present results seem to justify the conclusion that postoperative radiotherapy is not required in stage I, in any event. If a carcinoma has spread outside the ovaries, irradiation should always be considered if it is uncertain whether the entire neoplasm has been successfully removed. In cases of widespread malignancy the usefulness of irradiation can hardly be disputed. Preoperative radiotherapy is indicated at least in those cases in which the carcinoma has extended far into the pelvis, the purpose of the treatment being to reduce the amount of tissue to be excised. The same view was put forward by Long et al. (1967) Local administration of radium is useful in those cases in which the carcinoma is situated near the vaginal stump, or has extended into the uterus. This kind of treatment may be applied either pre or postoperatively depending on the case. Radioactive gold may be of value in cases where there is a suspicion that carcinomatous cells or minute metastases have remained in the abdominal cavity

On evaluating the merits of pre and postoperative radiotherapy it should be borne in mind that local radium treatment and advanced supervoltage therapy are more efficient than ordinary X-ray treatment. At the time covered by the present study all of the modern inventions in this field were not yet available Advanced irradiation techniques render it possible to use higher doses, and the modern methods enable precise centering on the affected area even in obese patients (Nieminen & Kotsalo 1966) The conclusions drawn, for instance from the present study concerning the merits of irradiation may therefore later prove wrong.

The use of cytotoxic drugs in the treatment of ovarian cancer cannot be evaluated on the basis of this study but our experience during the last few years speaks in favour of the view that they may be helpful in advanced cases, at least as a palliative measure.

REFERENCES

Allan, M & Hertig, A. Amer J Obstet Gynec 58 640, 1949

Benson, R., Sherman, R., Jr & Lucia, E. West J Surg 61 387 1953

Crainz, F Strahlentherapie 63 434 1938.

Helsel, E. V. Amer J Obstet Gynec 5 435 1946.

Hofman, D Zbl Gynäk 84 355 196_

Javert, C. T & Rascoe, R. R. Surg Clin N Amer 33 557 1953.

Kerr H. D. & Elkins, H. B. Amer J Roentgenol 66 184, 1951

Kjellgren, O Gynekologisk cancer, klinik och terapi. Almqvist & Wiksell, Stockholm, 1967

Latour J & Davis, B. Amer J Obstet Gynec 74 968, 1957

Lauren, P Grönroos, M Rauramo L & Lehto, J Duodecim (Helsinki) 84 864, 1968

Lindfors, O T be published in 1969

Long, R., Johnson, R & Sala, J Cancer (Philad.) 20 1195 1967

Müller J Die Krankheiten des Eierstockes. I Handbuch der speziellen pathologischen Anatomie und Histologie (ed. O Lubarsch & F Henke), VII III. Springer Berlin, 1937

Munnell, E. & Taylor H Amer J Obstet Gynec 58 943 1949

Munnell, E. Amer J Obstet Gynec 100 790 1968.

Nieminen, U & Kotsalo K. Ann Chir Gynaec Fenn 55 313, 1966

Nummers, C. on. Finska Läk-Sällsk. Handl 6, 720 1934

Orden, D an, McAlister W Zerne S & Morris, J Amer J Obstet Gynec 94 195 1966.

Pearse W H. & Behrman, S J Obstet and Gynec 3 3_, 1954

Platt, A. J. Rubenstone, A. I. & Hirsch, E. L. Amer J Obstet Gynec 84 375 1962.
Purola, E.: Acta Obstet Gynec Scand 42 Suppl. 2, 1963.
Randall, C. Obstet and Gynec 5 445 1955.
Santesson, L. & Kottmeier H General classification of ovarian tumours. In Ovarian Cancer (ed. F Gentil & A. C. Junqueira) Springer, Berlin, 1968 (UICC Monograph Series 11.)
Saxén, E. A. & Hakama, M.: End results studies on cancer of the ovary *I* International Symposium on End Results of Cancer Therapy Sandefjord, Norway September 16-20 1963 (ed. S. J Cutler), p. 135. (National Cancer Institute Monograph, 15.)
Vara, P. & Pankamaa, P Acta Obstet Gynec Scand 26 Suppl. 4, 1946.

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basis of a later series Munnell (1968) states that irradiation is required when a carcinoma has extended outside the ovaries and in these cases of stages I and II in which the histological structure of the tumour shows a low degree of differentiation. In the present series, surgical treatment alone seemed to yield better results than surgery plus irradiation (Table III) This obtains to both radical and conservative surgery The result was the same when the comparison was performed by stages, i.e. by comparing all stages together and by distinguishing stage I. It should be borne in mind, however that the same stage includes a number of more "favourable" cases in which radiotherapy is more likely to be abandoned. In other words, the group of patients treated by surgery alone includes a relatively greater number of "favourable" cases, which may influence the end result.

Opinions differ concerning the justification for postoperative radiotherapy but the majority of authors regard this as an indispensable adjunct to surgical treatment. Some investigators, however consider the value of irradiation as open to question (Saxén et al 1963) Latour & Davis (1957) were even able to show that the results in groups treated both surgically and by irradiation were poorer than the results obtained by surgical treatment alone The present results seem to justify the conclusion that postoperative radiotherapy is not required in stage I in any event If a carcinoma has spread outside the ovaries, irradiation should always be considered if it is uncertain whether the entire neoplasm has been successfully removed. In cases of widespread malignancy the usefulness of irradiation can hardly be disputed. Preoperative radiotherapy is indicated at least in those cases in which the carcinoma has extended far into the pelvis, the purpose of the treatment being to reduce the amount of tissue to be excised. The same view was put forward by Long et al. (1967) Local administration of radium is useful in those cases in which the carcinoma is situated near the vaginal stump or has extended into the uterus. This kind of treatment may be applied either pre- or postoperatively depending on the case. Radioactive gold may be of value in cases where there is a suspicion that carcinomatous cells or minute metastases have remained in the abdominal cavity

On evaluating the merits of pre and postoperative radiotherapy it should be borne in mind that local radium treatment and advanced supervoltage therapy are more efficient than ordinary X-ray treatment. At the time covered by the present study all of the modern inventions in this field were not yet available. Advanced irradiation techniques render it possible to use higher doses, and the modern methods enable precise centering on the affected area even in obese patients (Nieminen & Kotsalo 1966) The conclusions drawn, for instance, from the present study concerning the merits of irradiation may therefore later prove wrong.

The use of cytotoxic drugs in the treatment of ovarian cancer cannot be evaluated on the basis of this study but our experience during the last few years speaks in favour of the view that they may be helpful in advanced cases, at least as a palliative measure.

REFERENCES

Allan, M. & Hertig, A. Amer J Obstet Gynec *58* 640, 1949

Benson, R., Sherman, R., Jr & Lucia, E. West J Surg *61* 387 1953.

Crainz, F Strahlentherapie *63* 434 1938.

Hebel, E. V Amer J Obstet Gynec *52* 435 1946.

Hofman, D. Zbl Gynäk *84* 385 1962.

J vert, C. T & Rascoe, R. R. Surg Clin N Amer *33* 557 1953

Kerr H. D & Elkins, H. B. Amer J Roentgenol 66. 184, 1951

Kjellgren, O *Gynekologisk cancer, klinik och terapi.* Almqvist & Wiksell, Stockholm, 1967

Latou J & Davis, B. Amer J Obstet Gynec *74* 968, *1957*

Lauren, P Gronroos, M Rauramo L. & Lehto, J Duodecim (Helsinki) *84* 864 1968

Lindfors, O To be published in 1969

Long, R., Johnson, R. & Sala, J Cancer (Philad) 20. 1195 1967

Miller J Die Krankheiten des Eierstockes. *In* Handbuch der speziellen pathologischen Anatomie und Histologie (ed. O Lubarsch & F Henke) VII/*III. Springer* Berlin, 1937

Munnell, E. & T ylor H. Amer J Obstet Gynec *58.* 943, 1949

Munnell, E. Amer J Obstet Gynec *100*· 790, 1968

Nieminen, U & Kotsalo, K. Ann Chir Gynaec Fenn *55* 313 1966

Numers, C. von. Finska Läk-Sällsk Handl *76* 720, 1934.

Orden, D van, McAllister W Zerne, S. & Morris, J Amer J Obstet Gynec *94* 195 1966.

Pearse, W H & Behrman, S. J Obstet and Gynec *5* 32, 1954

Acta Obstet Gynec Scand 49: 57–59 1970

TREATMENT OF THE UMBILICAL CORD OF THE NEWBORN

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Abstract. Daily painting of the umbilical stump with Betadine® during the stay in the maternity ward reduced the incidence of umbilical infections. In clinical use a tiny rubber ring for closure of the cut umbilical cord proved more practical and cheaper than a clip, the use of the ring in conjunction with painting with Betadine® accelerated the separation of the stump.

At the State Hospital of Lapland closure of the umbilical cord with an aluminium umbilical clip (Lovset, 1930) was introduced 1957. Since some umbilical complications occurred, although these were in fact few and possibly due to technical errors in the application of the clip, closure of the stump with a rubber ring (Österlund, 1967) was tried toward the end of 1964. The rubber ring became popular among the midwives and children's nurses, and we soon started using Österlund's ring exclusively. Otherwise we did not change our earlier open treatment of the stump, i.e. daily bathing of the infant and daily painting of the stump and the surrounding skin with Betadine®. The Betadine® regimen was adopted 1964. In order to investigate whether the painting with Betadine® and/or the use of Österlund's rubber ring had influenced upon the time of separation of the umbilical stump and/or the rate of clinical umbilical infection, we compared three groups of infants, born in the winters of 1964 and 1965.

MATERIAL

In group I, Lovset's clip was used. In group II, Lovset clip was likewise used, and the umbilical stump was treated with Betadine®. In group III, the rubber ring of Österlund (Österlund, 1967) was used and the stump was treated with Betadine®.

All groups comprised a number of consecutive cases. Those cases were omitted in which information was incomplete in the following respects:

1. The infant had been discharged to the Children's Hospital and no information was available concerning the later state of the navel or the time when the stump was separated (about 10%).

2. The infant and the mother had been discharged at an early stage to their local hospital (Tötterman & Hakkila, 1967) and the time of separation of the umbilical stump was unknown (about 5%).

3. Our own record was incomplete with respect to the time of separation of the stump (about 5%).

4. Relevant information was not obtained from the maternity centre (less than 5%).

5. The infant was stillborn or died soon after birth (about 2%).

About one-fourth of the original cases had to be discarded, but this ought not to influence the results, since omission was due to chance and the proportion of cases omitted was about the same in all the three groups. All the deliveries in this series occurred in the winter. The occurrence of hospital infections was routinely assessed both clinically and by the aid of regular bacterial cultures from the babies and the staff. Throughout the period covered by this study the situation was satisfactory in this respect. The three groups should therefore be comparable.

RESULTS AND DISCUSSION

In Table I the results of the different methods of treatment are given according to our own records and to routine follow-up information sent by the various maternity centres to the Obstetric Department (Tötterman et al., 1966). The three groups are divided into four subgroups each on the basis of the birth weight (columns 2 and 3). The groups of prematures are small. This is mainly due to the fact that many prematures were admitted to the

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[2] The Hospitals have since been united under the name of Central Hospital of Lapland.

Betadine®: solutio externa, polyvidon. jod. 10 g, ad- dendo et aq. purificata. Leiras, Turku, Finland.

Moreover Bret et al. (1958) found a clear similarity between flora of the vaginal discharge and of the infant's infection. No significant difference was observed between maternal parity in the infected group and that in the whole series. The low frequency of umbilical infection in the low weight baby groups may be attributed to a longer average stay in hospital with a longer continued Betadine® treatment of the stump.

Column 7 gives the sex distribution of the infected cases. We were surprised to note that the frequency of umbilical infection was higher in girls. We have not been able to find a reasonable explanation of this phenomenon.

Among the above mentioned factors which might have influenced the occurrence of umbilical infection none seemed to afford any explanation of the fact that in group I the rate of infection was more than twice the rate in groups II and III. Since no such difference was observed between groups II and III the better result in these groups is probably due to the Betadine® treatment. The use of the rubber ring did not reduce the frequency of infection. No complications due to this treatment occurred, no skin reactions were reported, and the PBI values determined in some cases on discharge of the infant from the hospital were normal. Hence, Betadine® may safely be used for prophylactic painting of the umbilical stump. Considering the variety of methods described and rates of infection reported (Huntingford et al., 1961, Andersen et al., 1963, Henderson et al., 1964), the ideal treatment of the umbilical stump does not yet seem to have been developed. Our method did not entirely eliminate umbilical infection, either. However, the frequency was quite low and, with the exception of one case, infection was very slight, manifesting itself as an umbilical fungus or simple umbilical wetting.

As to the choice between a clip such as Løvset or some of the newer ones made of plastic and Österlund's rubber ring, we definitely prefer the rubber ring. It is, as a rule, easily applied, although its application on a very thick cord may be a bit of problem. However as far as we know there was not one cord, among over 2500, on which the ring could not be placed. The ring is also probably the cheapest and the least visible appliance available for closing the cord, and interferes the least with the care of the infant. Many mothers in our obstetrical ward said that they were afraid of the big metal clip and thought it would interfere with the nursing of the baby. The ring is also very secure, there was no case of late umbilical haemorrhage in over 2500 cases. Neligan et al. (1964) arrived at the same conclusions. These authors used a rubber band with which the stump was tied. They emphasized in particular that the elastic band promoted the separation of the stump. The Yearbook of Pediatrics commented upon their method as follows: "There is nothing new in the use of an elastic band for cord tie" mentioning that rubber bands have been used highly successfully for tying the cord at the Boston Lying-in Hospital for over 20 years.

REFERENCES

Andersen, H. J., Holm, S. S. & Wiberg, J.: *Sv Läk Tidn 60* 99, 1963.

Bret, J., Coupe, C., Solle, R. & Marchand, H.: Presse Médicale *66* 937, 1958.

Forsham, L. Arch Dis Childh *32*, 23, 1964.

Henderson, R. J., Chalmers, J. A. & Wood, J.: J Obstet & Gynaec Brit C'lth *71* 443, 1964.

Huntingford, P. J., Welch, G., Glass, U. & Wetherley-Mein, G.: J Obstet & Gynaec Brit Cwlth *68* 179, 1961.

Løvset, J.: Acta Obstet Gynec Scand *12* 150, 1932.

Neligan, G. A., Parkin, J. M. & Paul, C.: Arch Dis Childh *39* 630, 1964.

Tötterman, L. E., Forsström, E., Rimö, P. & Heikkilä, A.: Suom Lääk-L *21* 2437, 1966.

Tötterman, L. E. & Hanakka, M.: Suom Lääk L *22* 1507, 1967.

Zilliacus, H. & Tötterman, L. E.: *Gynaecologia* *135* 353, 1953.

Yearbook of Pediatrics 1965–1966, 7. Yearbook Medical Publ. Inc., Chicago.

Österlund, K.: Duodecim *83* 81, 1967.

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Table I. *Three groups of 200 infants listed according to birth-weight. The time of separation of the umbilical stump. Incidence of clinical umbilical infections in the various subgroups*

Methods of treatment	Distribution according to weight (g)	No. of patients	Average time of separation of umbilical stump	No. of cases of umbilical infection	Average time of separation of umbilical stump in infected cases (days)	Incidence of cord infection (%)	Sex distribution in infected cases (%)
Lovset's clip	–2500	5	5	0	?	?	
	2501–3000	30	7.4	3	8.0	10	
	3001–3500	76	6.8	9	8.5	11	
	3501–	89	6.8	15	8.5	17	
	Group I	200	6.9	27	8.4	13.5	11/16
Lovset's clip + Betadine®	–2500	3	5	0	?	?	
	2501–3000	21	5.1	2	5.0	10	
	3001–3500	64	6.1	3	7.7	5	
	3501–	112	6.5	6	6.8	5	
	Group II	200	6.2	11	6.7	5.5	4/7
Rubber ring + Betadine®	–2500	6	6	0	?	?	
	2501–3000	33	5.8	0	?	?	
	3001–3500	60	5.7	3	6.6	5	
	3501–	101	6.0	6	6.2	6	
	Group III	200	5.9	9	6.4	4.5	2/7
All groups together	–2500	14	5	0	?	?	
	2501–3000	84	6.2	5	6.8	6.0	
	3001–3500	200	6.2	15	7.9	7.5	
	3501–	302	6.4	27	7.6	8.9	
	Group I+II+III	600	6.3	47	7.8	7.8	17/30

premature ward of the Children's Hospital. The premature groups were included in the present series, however, because we wished to find out wether the prematures had been particularly susceptible to umbilical infection.

As is seen in column 4, there are only slight differences in the time of separation of the umbilical stump between the different weight groups. Treatment group I has the longest mean time of separation, group III the shortest. As regards the distribution of the individual times of separation, there are no differences between group I and group II, nor between group II and group III ($p < 0.05$). On the other hand, there is a highly significant shift towards shorter times in group III as compared with group I ($p < 0.001$). It may therefore be assumed that the use of Österlund's rubber ring in conjunction with painting with Betadine® to some extent accelerated the separation, as compared with those cases in which only a metal clip was used.

In almost all treatment and weight groups there is delay in the time of separation of the umbilical stump in the infected cases as compared with those in which no infection is recorded. Delayed separation of the stump may at any rate partly be due to infection (Forsham, 1964).

The highest rate of infection was observed in group I, in which an aluminium clip was used and no Betadine® painting of the stump was performed. When the clip was used in conjunction with treatment with Betadine® the result was much better. It was not improved when the clip was replaced by the rubber ring.

When the cases of umbilical infection were compared with the whole series, no differences were observed in the period of hospitalization and the frequency of vaginal examinations in the mother. No correlation was observed between umbilical infection and the interval between rupture of the membranes and delivery of the child. Infections of the mother showed no relationship, either with umbilical infection. Previously Zilliacus & Tötterman (1953) found a positive correlation between urinary infection in the mother and infections of the newborn. Neither did leucorrhea, as recorded in the routine delivery reports, affect the incidence of umbilical infections in this series, although during delivery the umbilical cord and vagina come into close contact with one another

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COAGULATION AND FIBRINOLYSIS IN RHESUS-IMMUNIZED MOTHERS AND THEIR ERYTHROBLASTOTIC NEWBORN INFANTS

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Abstract A study of the parameters of coagulation and fibrinolysis in Rhesus D immunized mothers and their erythroblastotic infants gave the following results, on comparison with normal women delivered at term and their newborn infants and with prematurely delivered women and their newborn infants:

A *Mothers* No influence of the Rhesus immunization upon the parameters of coagulation or fibrinolysis.

B *Newborn infants*: With increasing severity of erythroblastosis decreasing platelet count and at the same time an increasing content of clot-promoting components in the plasma. In addition, reduced content of PP and factor V but unchanged fibrinogen.

Fibrinolytic activity was also reduced in erythroblastotic newborn infants

The causes of these changes are discussed.

There have been no reports on the parameters of coagulation and fibrinolysis in Rhesus-immunized mothers, but in communications on newborn infants with erythroblastosis it is often pointed out, that one of the complications is a coagulation disorder leading to a haemorrhagic diathesis which may manifest itself as petechiae, purpura, pulmonary haemorrhage etc. However these observations are based upon very few investigations relying mainly on platelet counts and the determination of blood fibrinogen.

The present investigation was designed to study the influence of Rhesus immunization upon the maternal as well as infant's parameters of coagulation and fibrinolysis.

PREVIOUS INVESTIGATIONS

The following review of the literature will deal, as far as possible only with the results of analyses of samples taken from mother and infant at the time of birth. In addition, some studies described the influence of exchange transfusion upon coagulation in newborn infants with erythroblastosis. The results of these studies will be reported in a subsequent paper

The individual investigations will be reported in relation to the three phases of coagulation.

First phase of coagulation

Platelets. In 10 erythroblastotic newborn infants Heyn et al. (1952) found within the first 6 hours of birth a platelet count averaging 240 000/cmm. Hartmann et al. (1955) reported thrombocytopenia in three newborn infants with severe erythroblastosis. The exact time of sampling or the exact platelet count are not stated in their reports, or in that of Stefanini & Dameshek (1955) who mention thrombocytopenia as a common finding in erythroblastosis. In study of 325 newborn infants having erythroblastosis due to Rhesus incompatibility—performed in all cases before exchange transfusion, but the exact time not stated—Moulinier (1967) found 54 7 % to have a reduced platelet count (between 100,000 and 140,000/cmm) and 3 7 % severe thrombocytopenia (below 80 000/cmm). Similarly Ekert & Mathew (1967) studying 17 newborn infants, found thrombocytopenia (below 100,000/cmm) in severe cases, assessed on the basis of the bilirubin content of the cord. The samples were drawn from 2 to 24 hours before exchange transfusion.

There have been no reports relating to the other factors of the first phase of coagulation (factors VIII IX, XI and XII).

Second phase of coagulation

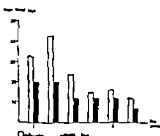
In 1939 Dam et al. demonstrated considerable hypoprothrombinaemia in an erythroblastotic infant aged 4 hours. Furthermore, Hartmann et al.

Gynecologists!

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Contraindications
Caution is needed when CYKLOKAPRON is used for patients with renal insufficiency because of the risk of accumulation and in massive hematuria from the upper urinary tract, since in few cases ureteric obstruction has been reported.
In patients with pronounced thrombotic tendency particular care should be taken, unless the patient can be treated simultaneously with anticoagulants. The safety of CYKLOKAPRON in pregnancy has yet to be confirmed clinically.

Side effects
Occasionally gastrointestinal disturbance and giddiness, which disappear when the dose is decreased.

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The following doses are recommended
General fibrinolysis: ampoules of 5 ml (2 0.5 g) intravenously 3–4 times daily
Prostatectomy 1–2 ampoules of 5 ml (0.5–1 g) intravenously 2–3 times daily (first dose given during operation) for the first 3 days after operation thereafter 2–3 tablets (1–1.5 g) 2–3 times daily until macroscopic hematuria is no longer present.
Hematuria and so-called essential hematuria. 3 tablets (1–1.5 g) –3 times daily until macroscopic hematuria is no longer present.
Menorrhagia tablets (1 g) 3–6 times daily as required, for 3–6 days. Treatment should start only when bleeding has become profuse.

Nilsson, L. Rybo G. Treatment of menorrhagia with an antifibrinolytic agent, tranexamic acid (AMCA). A double blind investigation Acta Obstet Gynecol. Scand. 46 (1967) p. 572.

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Table I. *Results of coagulation and fibrinolysis studies in normal and Rhesus-immunized women immediately after delivery*

Tests, see Methods	Normal women, delivery at term, Group 4		Rhesus immunized women						Normal women premature delivery Group 5	
			Group 1		Group 2		Group 3			
	$\bar{x}$ and n	Range est. S.D.	$\bar{x}$ and n	Range est. S.D	$\bar{x}$ and n	Range est. S.D	$\bar{x}$ and n	Range est. S.D.	$\bar{x}$ and n	Range est. S.D.
Platelets (thousands per cu. mm)	221 20	142–383 ±70	207 10	166–258 ±30	184 14	78–241 ±47	205 7	156–239 ±31	231 10	139–448 ±90
Proaccelerin (%)	122 20	75–210 ±37	107 10	76–160 ±25	114 14	90–138 ±15	112 7	63–158 ±26	101 10	75–125 ±17
Prothrombin time (sec)	17 20	14–20 ±1.4	17 10	16–19 ±0.8	17 14	14–20 ±1.4	18 7	16–19 ±0.9	18 10	15–20 ±1.7
P and P (%)	227 20	165–340 ±51	174 10	145–210 ±20	170 14	140–205 ±21	174 7	140–210 ±24	178 10	115–245 ±44
Partial thromboplastin time (sec)	73 19(¹)	63–81 ±4.0	75 10	66–79 ±3.5	75 14	67–85 ±4.9	74 6(¹)	73–78 ±2.3	75 10	67–85 ±5.0
Thrombin time (sec)	8 20	5–10 ±1.6	7 10	6–9 ±1.0	7 14	5–8 ±0.8	7 7	6–12 ±2.6	6 10	5–8 ±1.0
Fibrinogen (mg per 100 ml)	502 20	380–690 ±80	465 10	375–680 ±116	492 14	400–615 ±75	483 7	330–565 ±78	515 10	440–630 ±57
Haematocrit ( )	41 20	34–46 ±3.2	40 10	35–45 ±4.0	42 14	40–46 ±2.4	40 7	35–45 ±3.7	41 10	35–55 ±1.8
Untreated fibrin plates, untreated plasma (sq mm)	0 20	0 ±0	0 10	0 ±0	0 14	0 ±0	0 7	0 ±0	0 10	0 ±0
Untreated fibrin plates, Euglobulins (sq mm)	37 20	11–75 ±17	17 10	9–29 ±17	26 14	9–65 ±16	33 7	16–71 ±20	30 10	0–93 ±35
Heated fibrin plates, untreated plasma (sq mm)	0 20	0 ±0	0 10	0 ±0	0 14	0 ±0	0 7	0 ±0	0 10	0 ±0
Heated fibrin plates, Euglobulins (sq mm)	25 20	9–78 ±16	20 10	4–36 ±9.0	30 14	11–49 ±12	25 7	16–42 ±9.8	21 10	0–40 ±14
Plasminogen (µg Cu-Tyrosine per ml)	168 20	126–208 ±21	179 10	125–198 ±23	175 14	126–206 ±21	179 7	140–228 ±36	169 10	126–198 ±18

$\bar{x}$ arithmetic average, n number of estimations.
Range range of individual results (x), est. S.D. estimated standard deviation, $\sqrt{\Sigma(x-\bar{x})^2/(n-1)}$.
Clotting times shorter than 60 sec in the partial thromboplastin time test are not included in the calculations.
They were observed in two samples (¹)

Group 4

Twenty normal parturient women at term and their newborn infants.

Group 5

Ten normal women who went into labour an average of 5 weeks before term (range 4–7 weeks) and their premature infants, birth weight averaged 2270 g (range 2020–2440 g). In these last two groups vitamin K was administered and blood samples drawn just as in the first three groups. The control series has previously been described (Nielsen, 1969 a; 1969 d).

The maternal blood samples were removed from an ante-cubital vein after application of a light tourniquet. In the newborn infants the cord was secured close to the skin and a disposable plastic catheter was inserted through the umbilical vein. The samples were used only if there was a free flow of blood through the catheter. The technique of the sampling and further processing of the samples have been described previously. Determinations of recalcification time, thromboplastin activation test (TAT) two- and three-stage, partial thromboplastin time (PTT), thrombin time, prothrombin time (Quick), factor V prothrombin-proconvertin (PP), fibrinogen content and measurement of fibrinolytic activity in the plasma and in iso-electrically precipitated plasma on untreated fibrin

(1955) found reduced factor II (prothrombin) *factor V (proaccelerin)* and factor VII (proconvertin) in the three erythroblastotic infants mentioned above, but here again the tests were made rather a long time after birth.

In contradistinction Heyn et al. (1952) found *the same prothrombin level* in normal and erythroblastotic infants within the first 6 hours of birth. The same result was reported by de Bruijne & v Creveld (1955) as far as factors II and VII were concerned, while factor V was found to be greatly reduced *in 27 full-term infants with* "haemolytic disease" Their analyses were done on samples drawn when exchange transfusion was being started, but the exact *time in relation to* birth is not stated.

Third phase of coagulation

Fibrinogen Stimulated by a case report by Rice (1953) on hypofibrinogenaemia in a newborn premature infant with erythroblastosis Engström & Kager (1961) performed a study of the fibrinogen content in the plasma within the first 2 hours of birth in ten erythroblastotic newborn infants. On comparison with a group of normal newborn infants they could not demonstrate any difference. It is apparent also from their report that the fibrinogen content was independent of the haematocrit. These results have been confirmed in a *subsequent study by Ekert & Mathew (1967)*

Fibrinolysis Studies of fibrinolytic activity in newborn infants with erythroblastosis have not been reported.

MATERIAL AND METHODS

The present analyses were based upon blood samples from the following five groups.

Group 1

Ten Rhesus D negative women in whom Rhesus D antibody (in two cases Rhesus C+D antibody) had been demonstrated, but in most cases of low titre. The indirect Coombs test averaged 1:36 (range 1:1–1:256) *The blood samples were drawn within* the first 20 min after delivery All but two of the mothers had received prophylactic vitamin K in the form of menadione tablets in a dosage as previously described (Nielsen, 1969). Labour was induced, on average, 1 week before term (range 0–2 weeks) by intranasal oxytocin followed by rupture of the membranes or merely by rupturing the membranes. However in one case the delivery occurred spontaneously at term. In all cases the pregnancies, deliveries, and puerperal *periods were otherwise normal.*

Blood samples were also drawn *from these mothers* ten newborn infants within the first 15 min of birth. *Rhesus D antibody* was demonstrated in all the infants, but in a quantity so small that exchange transfusion was not necessary during the first 3 days. *(One infant had an exchange transfusion on the fourth day* because of an increasing bilirubin level.) The direct Coombs test was moderately positive in three cases, weaker in the others. No infant was anaemic (haematocrit *averaging* 51% range 45–58%). The average birth weight was 3390 g (range 2880–3940 g). No infant exhibited signs of other complications.

Group 2

Fourteen Rhesus D *negative women in whom* Rhesus D antibody (in four cases Rhesus C+D and in one case D+E) had been demonstrated, but of a more marked degree than in group 1 The indirect Coombs test averaged *1:240* (range 1:1–1:2048). Vitamin K prophylaxis as well as blood sampling were as in group 1. Labour was induced, on average, 3 weeks before term (range 1–4 weeks) as described above. The pregnancies, deliveries, and puerperal periods were otherwise normal.

Blood samples were also drawn from these patients' 15 newborn infants within the first 20 min after birth. Considerable quantities of Rhesus D antibody were demonstrated in the infants (direct Coombs test moderately positive in one case and moderately to strongly positive in another while in twelve cases it was strongly positive or very strongly positive). Several of the newborn infants were anaemic (haematocrit averaging 48% range 41–60%), so that, mainly because of the direct *Coombs test and the anaemia, exchange* transfusion *had to be done in all cases within the first 9* hours of birth. The average birth weight was 3080 g (range 2100–4200 g). None of the infants exhibited other complications.

Group 3

Seven Rhesus D negative women in whom Rhesus D antibody (in four cases C+D) had been demonstrated and in whom the indirect Coombs test averaged 1:630 (range 1:16–1:2048). When also correlated with their history these findings led to the induction of labour, on average, 3½ weeks before term (range 2–5 weeks) after otherwise uncomplicated pregnancies. However, three patients had an elective caesarean section because of rapidly progressing immunization and one had a section because of failure to progress in labour All had received prophylactic vitamin K. The *puerperium* was uneventful.

Blood samples were drawn also from these mothers' seven severely erythroblastotic infants (direct Coombs test strongly positive in four and very strongly positive in three) all of whom were also severely anaemic. Haematocrit averaged 31% (range 23–38%). The blood samples were drawn within the first 25 min after birth, and all the infants had exchange transfusion within the first 6 hours. The average birth weight was 2730 g (range 1380–4300 g). Two infants died within the first 24 hours. Post-mortem *diagnosis: Erythroblastosis* foetalis. The infants exhibited no other complications during their stay in the department.

The following two groups served as controls:

Table I *Results of coagulation and fibrinolysis studies in normal and Rhesus-immunized women immediately after delivery*

Tests, see Methods	Normal women, delivery at term, Group 4		Rhesus immunized women Group 1		Rhesus immunized women Group 2		Rhesus immunized women Group 3		Normal women premature delivery Group 5	
	$\bar{x}$ and	Range est. S.D.	$\bar{x}$ and	Range est. S.D.	$\bar{x}$ and	Range est. S.D.	$\bar{x}$ and	Range est. S.D.	$\bar{x}$ and	Range est. S.D.
Platelets (thousands per cu. mm)	221 20	142 383 ±70	207 −10	166–258 ±30	184 −14	78–241 ±47	205 −7	156–259 ±31	231 −10	139–448 ±90
Proaccelerin (%)	122 20	75–210 ±37	107 10	76–160 ±25	114 −14	90–138 ±15	112 −7	63–158 ±26	101 −10	75–125 ±17
Prothrombin time (sec)	17 20	14–20 ±1 4	17 −10	16–19 ±0.8	17 −14	14–20 ±1 4	18 7	16–19 ±0.9	18 −10	15–20 ±1 7
P and P ( )	227 20	163–340 ±31	174 −10	145–210 ±20	170 −14	140–205 ±21	174 −7	140–210 ±24	178 −10	115–245 ±44
Partial thromboplastin time (sec)	75 19(1)	65–81 ±4 0	75 −10	66–79 ±3.5	75 −14	67–85 ±4.9	74 6(1)	73–78 ±2 3	75 −10	67–85 ±5.0
Thrombin time (sec)	8 20	5–10 +1.6	7 −10	6–9 ±1.0	7 14	5–8 ±0 8	7 7	6–12 ±2.6	6 −10	5–8 ±1.0
Fibrinogen (mg per 100 ml)	502 20	380–690 +83	465 10	373–680 ±116	492 −14	400–615 ±75	483 −7	330–565 ±78	515 −10	440–690 +57
Haematocrit ( )	41 20	34–46 ±3.2	40 10	33–45 ±4 0	42 −14	40–46 ±2.4	40 −7	35–45 ±3.7	41 10	35–53 ±1.8
Unheated fibrin plates, untreated plasma (sq mm)	0 20	0 _0	0 10	0 ±0	0 −14	0 ±0	0 7	0 ±0	0 −10	0 ±0
Unheated fibrin plates, Euglobulins (sq mm)	37 20	11 75 ±17	17 10	9–29 ±17	26 −14	9–65 ±16	33 7	16–71 ±20	30 −10	0–93 ±35
Heated fibrin plates, untreated plasma (sq mm)	0 20	0 ±0	0 10	0 ±0	0 14	0 ±0	0 7	0 ±0	0 −10	0 ±0
Heated fibrin plates, Euglobulins (sq mm)	25 20	9–78 ±16	20 10	4–36 ±9 0	30 14	11–49 ±12	25 7	16–42 ±9 8	21 10	0–40 ±14
Plasminogen (μg Cu-Tyrosine per ml)	168 20	126–208 _21	179 10	125–198 23	175 14	126–206 ±21	179 7	140–228 ±36	169 −10	126–198 ±18

$\bar{x}$ arithmetic average   number of estimations.
Range range of individual results (x), est. S D estimated standard deviation. $\sqrt{\Sigma(\ \ \bar{x})^2/(n-1)}$.
Clotting times shorter than 60 sec in the partial thromboplastin time test are not included in the calculations.
They were observed in two samples(¹).

Group 4

Twenty normal parturient women at term and their newborn infants.

Group 5

Ten normal women who went into labour an average of weeks before term (range 4–7 weeks) and their premature infants, birth weight averaged 2270 g (range 920–440 g). I these last two groups vitamin K was administered and blood samples drawn just as in the first three groups. The control series has previously been described (Nielsen, 1969 c 1969 d).

The maternal blood samples were removed from an ante-cubital vein after application of light tourniquet. In the newborn infants the cord was ligated close to the skin and disposable plastic catheter was inserted through the umbilical vein. The samples were used only if there was free flow of blood through the catheter. The technique of the sampling and further processing of the samples have been described previously. Determination of recalcification time, thromboplastin activation test (TAT) two- and three-stage, partial thromboplastin time (PTT), thrombin time, prothrombin time (Quick), factor V prothrombin-proconvertin (PP), fibrinogen content and measurement of fibrinolytic activity in the plasma and in iso-electrically precipitated plasma on unheated fibrin

Table II *Results of coagulation and fibrinolysis studies in normal and erythroblastotic infants*

	Normal infants, delivery at term, Group 4		Erythroblastotic infants						Premature infants, Group 5	
			Group 1		Group 2		Group 3			
Tests, see Methods	x̄ and n	Range est. S.D	x̄ and n	Range est. S.D	x̄ and n	Range est. S.D	x̄ and n	Range est. S.D.	x̄ and n	Range est. S.D.
Platelets (thousands per cu. mm)	371[b] n = 20	280–604 ±82	352 = 10	251–486 ±67	305 n = 15	90–449 ±104	168 = 7	24–279 ±93	307 n = 10	174–625 ±144
Proaccelerin (%)	122 n = 20	82 160 ±30	90 n = 10	55–125 ±21	94 = 15	63–120 ±17	84 n = 7	48–105 ±20	92 = 10	59–115 ±21
Prothrombin time (sec)	19 n = 20	18–21 ±0.9	20 n = 10	18–22 ±1.3	19 = 15	16–21 ±1.4	19 n = 7	17 21 ±1.3	19 = 10	17–23 ±2.1
P and P (%)	90 n = 20	62–150 ±21	54 n = 10	27–82 ±19	58 = 15	39–86 ±14	50 n = 7	27–65 ±14	44 = 10	27–78 ±16
Partial thromboplastin time (sec)	92 n = 20	79–135 ±12	96 n = 10	81 118 ±14	93 = 15	82 130 ±13	112 n = 7	80–211 ±46	11 = 10	97–144 ±15
Thrombin time (sec)	14 n = 20	9–19 ±2.5	13 n = 10	9 21 ±3.8	13 n = 15	9–21 ±3.0	15 n = 7	10– 4 ±5.4	10 = 10	7–14 ±2.3
Fibrinogen (mg per 100 ml)	239 n = 20	230–345 ±51	209 = 10	165– 45 ±27	221 = 15	135–325 ±57	219 n = 7	130–315 ±59	264 = 10	140–378 ±67
Haematocrit (%)	56 n = 20	46–62 ±3.6	51 n = 10	45–58 ±3.9	48 n = 15	41–60 ±6.6	31 n = 7	3–38 ±6.5	56 = 10	47–65 ±5.6
Untreated fibrin plates, untreated plasma (sq. mm)	74 n = 20	26–245 ±51	52 n = 10	0–87 ±32	33 n = 15	0–84 ±32	23 = 7	0–81 ±32	38 = 10	0–54 ±22
Untreated fibrin plates, Euglobulins (sq. mm)	283 n = 20	107–576 ±155	189 n = 9	36–361 ±115	168 = 15	11–440 ±127	110 n = 7	0–760 ±106	211 = 10	25–391 ±104
Heated fibrin plates, untreated plasma (sq mm)	5 n = 20	4–49 ±10	17 = 10	0–36 ±11	14 = 15	0–25 ±9.7	10 n = 7	0–5 ±11	12 n = 10	0–25 ±8.3
Heated fibrin plates, Euglobulins (sq mm)	38 n = 20	25–54 ±8.2	23 = 9	9–23 ±5.3	26 = 15	4–36 ±8.6	21 n = 7	0–36 ±14	27 = 10	1–49 ±1
Plasminogen (μg Co-Tyrosine per ml)	61 = 20	35–104 ±19	57 = 10	17–80 ±18	58 = 15	27–74 ±14	52 n = 7	23–70 ±20	33 = 10	17–46 ±1

See footnote to Table I

[b] The platelet count is based upon a re-investigation of another group of newborn children cf. Nielsen (1969).

plates (standard plates) as well as on heated fibrin plates, plasminogen, haematocrit, and platelet counts were also performed as described previously (Nielsen, 1969 a).

RESULTS

The results of the *studies of coagulation and fibrinolysis* are listed in Tables I and II while Figs. 1–10 give the results for TAT and recalcification times.

To elucidate whether a difference exists between mildly and severely *Rhesus-immunized mothers* groups 1 2, and 3 were compared. This comparison showed no significant differences, either in the parameters of coagulation or of fibrinolysis. Moreover the course of TAT two- and three-stage as well as the recalcification time were practically identical.

Thereafter group 3 (that with the most severe Rhesus immunization) was compared with group 4 and 5 to demonstrate a difference, if any between Rhesus-immunized mothers on the one hand and normal mothers delivered at term and normal mothers delivered prematurely on the other The PP in the Rhesus immunized mothers was lower than in the normal mothers at term ($p < 0.001$) but equal to that in prematurely delivered normal mothers. Apart from this, no significant differences were demonstrated, either in the parameters of coagulation or of fibrinolysis. There seems to be a tendency to a somewhat more rapid

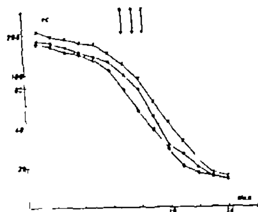


Fig. 1. Thromboplastin activation curve of peripheral blood drawn immediately after delivery from 20 normal women at term. — 20 normal adult women, two-stage TAT ●—● 20 normal women, two-stage TAT immediately after delivery ○—○ 20 normal women, three-stage TAT immediately after delivery

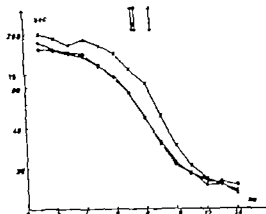


Fig. 3. Thromboplastin activation curve of peripheral blood drawn immediately after delivery from 14 women with moderate Rhesus immunization (group 2). — 14 normal adult women, two-stage TAT ●—● 14 women, two-stage TAT immediately after delivery ○—○ 14 women, three-stage TAT immediately after delivery

course of the TAT two-stage in severely Rhesus-immunized mothers, but this was significant only for t_1 ($0.01 > p > 0.001$) on comparison with normal mothers delivered at term. On comparison with the normal prematurely delivered mothers, on the other hand, there were no significant differences. The content of clot-promoting components in the plasma, judging by the TAT three-stage, was practically identical in all five groups.

By comparing groups 1, 2, and 3 it is possible to demonstrate, moreover, whether the parameters of coagulation and fibrinolysis of the newborn infants alter with increasing severity of the *erythroblastosis*. In groups 1 and 2 there were no significant changes, either the parameters of coagulation or of fibrinolysis, while group 3 showed marked decrease in the platelet count ($p < 0.001$), and at the same time the TAT two-stage ran a more rapid course, with a shortened t, t, T_{max}, and recalcification time. However, the changes are

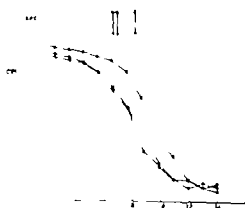


Fig. Thromboplastin activation curve of peripheral blood drawn immediately after delivery from 10 women with mild Rhesus immunization (group 1). — 10 normal adult women, two-stage TAT ●—● 10 women, two-stage TAT immediately after delivery ○—○ 10 women, three-stage TAT immediately after delivery

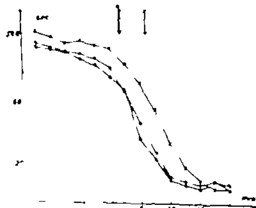


Fig. 4. Thromboplastin activation curve of peripheral blood drawn immediately after delivery from 7 women with severe Rhesus immunization (group 3). — 7 normal adult women, two-stage TAT ●—● 7 women, two-stage TAT immediately after delivery ○—○ 7 women, three-stage TAT immediately after delivery

Table II. *Results of coagulation and fibrinolysis studies in normal and erythroblastotic infants*

	Normal infants, delivery at term, Group 4		Erythroblastotic infants						Premature infants, Group 5	
			Group 1		Group 2		Group 3			
Tests, see Methods	x̄ and n	Range est. S.D	x̄ and n	Range est. S.D	x̄ and n	Range est. S.D	x̄ and n	Range est. S.D	x̄ and n	Range est. S.D
Platelets (thousands per cu. mm)	371[b] n = 20	280–604 ±82	352 n = 10	251–486 ±67	305 n = 15	90–449 ±104	168 n = 7	24–279 ±93	307 n = 10	[illegible] ±144
Proaccelerin (%)	122 n = 20	82–160 ±30	90 n = 10	55–125 ±21	94 n = 15	63–120 ±17	84 n = 7	48–105 ±20	92 n = 10	59–10[illegible] ±21
Prothrombin time (sec)	19 n = 20	18–21 ±0.9	20 n = 10	18–22 ±1.3	19 n = 15	16–21 ±1.4	19 n = 7	17–21 ±1.3	19 n = 10	17–23 ±21
P and P (%)	90 n = 20	62–150 ±21	54 n = 10	27–82 ±19	58 n = 15	39–86 ±14	50 n = 7	27–65 ±14	44 n = 10	27–7[illegible] ±16
Partial thromboplastin time (sec)	92 n = 20	79–135 ±12	96 n = 10	81–118 ±14	93 n = 15	82–130 ±13	112 n = 7	80–211 ±46	112 n = 10	97–144 ±15
Thrombin time (sec)	14 n = 20	9–19 ±2.5	13 n = 10	9–21 ±3.8	13 n = 15	9–21 ±3.0	15 n = 7	10–24 ±5.4	10 n = 10	7–14 ±2.3
Fibrinogen (mg per 100 ml)	239 n = 20	230–345 ±51	209 n = 10	165–245 ±[illegible]7	221 n = 15	135–325 ±57	219 n = 7	130–315 ±59	264 n = 10	140–37[illegible] ±67
Haematocrit (%)	56 n = 20	46–62 ±3.6	51 n = 10	45–58 ±3.9	48 n = 15	41–60 ±6.6	31 n = 7	23–38 ±6.5	56 n = 10	47–65 ±5.6
Untreated fibrin plates, untreated plasma (sq mm)	74 n = 20	26–245 ±51	5 n = 10	0–87 ±32	33 n = 15	0–84 ±32	23 n = 7	0–81 ±32	38 n = 10	0–54 ±22
Untreated fibrin plates, E globulins (sq mm)	283 n = 20	107–576 ±155	189 n = 9	36–361 ±115	168 n = 15	11–440 ±127	110 n = 7	0–260 ±106	211 n = 10	25–391 ±104
Heated fibrin plates, untreated plasma (sq mm)	23 n = 20	4–49 ±10	17 n = 10	0–36 ±11	14 n = 15	0–25 ±9.7	10 n = 7	0–[illegible]5 ±11	12 n = 10	0–25 ±8.3
Heated fibrin plates, E globulins (sq mm)	38 n = 20	25–54 ±8.2	23 n = 9	9–[illegible]5 ±5.3	26 n = 15	4–36 ±8.6	21 n = 7	0–36 ±14	27 n = 10	1–49 ±12
Plasminogen (µg Cu-Tyrosine per ml)	61 n = 20	35–104 ±19	57 n = 10	17–80 ±18	58 n = 15	27–74 ±14	52 n = 7	[illegible]3–70 ±20	33 n = 10	17–46 ±12

See footnote to Table I.
[b] The platelet count is based upon a re-investigation of another group of new-born children, cf Nielsen (1969).

plates (standard plates) as well as on heated fibrin plates, plasminogen, haematocrit, and platelet counts were also performed as described previously (Nielsen, 1969).

RESULTS

The results of the *studies of coagulation and fibrinolysis* are listed in Tables I and II, while Figs. 1–10 give the results for TAT and recalcification times.

To elucidate whether a difference exists between mildly and severely *Rhesus-immunized mothers* groups 1, 2, and 3 were compared. This comparison showed no significant differences, either in the parameters of coagulation or of fibrinolysis. Moreover, the course of TAT two- and three-stage as well as the recalcification time were practically identical.

Thereafter group 3 (that with the most severe Rhesus immunization) was compared with groups 4 and 5 to demonstrate a difference, if any, between Rhesus-immunized mothers on the one hand and normal mothers delivered at term and normal mothers delivered prematurely on the other. The PP in the Rhesus-immunized mothers was lower than in the normal mothers at term ($p < 0.001$), but equal to that in prematurely delivered normal mothers. Apart from this, no significant differences were demonstrated, either in the parameters of coagulation or of fibrinolysis. There seems to be a tendency to a somewhat more rapid

they were more obvious, and a number of new changes: a reduced PP ($p < 0.001$), factor V ($0.01 > p > 0.001$), and platelet count ($p < 0.001$) as well as reduced fibrinolytic activity by all four measuring methods: unprecipitated plasma on standard plates ($0.05 > p > 0.0?$), iso-electrically precipitated plasma on standard plates ($0.01 > p > 0.001$), unprecipitated plasma on heated fibrin plates ($0.01 > p > 0.001$), and iso-electrically precipitated plasma on heated fibrin plates ($p < 0.001$). The course of the TAT two-stage had become more rapid, with a shortened t_1 ($0.01 > p > 0.001$) and a tendency to shortened t_1, T_{max}, and recalcification time. The course of the TAT three-stage also showed an increased content of clot promoting components in the plasma.

Since the infants with severe erythroblastosis ha e a low birth weight (2830 g) and were born, on a erage 3½ weeks prematurely they were also compared with normal premature babies (group 5) with an average birth weight of 2260 g and born about 5 weeks before term. This showed the individual parameters of coagulation and fibrinolysis to be in the same range, except for the platelet count which was reduced in the erythroblastotic infants ($0.05 > p > 0.02$). In addition the course of the TAT two-stage was considerably accelerated in these infants, with significant shortening of t ($0.05 > p > 0.02$), T_{max} ($0.05 > p > 0.02$) t_{max} ($0.05 > p > 0.0?$), and recalcification time ($p < 0.001$) In accordance with these findings, the course of the TAT three-stage test indicated a

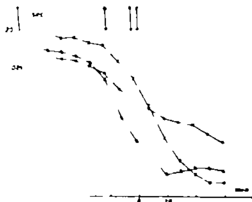


Fig. Thromboplastin activation curve of venous cord blood from 7 severely erythroblastotic infants (group 3) — 7 normal adult women, two-stage TAT ●—● 7 erythroblastotic infants, two-stage TAT O—O 7 erythroblastotic infants, three-stage TAT



Fig. 10 Thromboplastin activation curve of venous cord blood from 10 premature infants (group 5). — 10 normal adult women, two-stage TAT ●—● 10 premature infants, two-stage TAT O—O 10 premature infants, three-stage TAT

considerably increased content of clot-promoting components in the plasma.

DISCUSSION

The results submitted above show that *immunization of pregnant women by Rhesus D antibody* exerts no influence upon the maternal parameters of coagulation or fibrinolysis, not even in the case of massive immunization (group 3). The tendency to premature delivery f Rhesus-immunized mothers may contribute to the reduction in PP (174%) when compared with normal mothers at term (227%), cf. e g. Nielsen (1969 *d*). Since the PP was calculated by the aid of dilution curves plotted on logarithmic paper the uncertainty is most marked at high values, and this too may have been contributory

The content of clot promoting components in the maternal plasma will not be discussed further here, as the various theories advanced to explain this phenomenon hav been discussed in a previous paper (Nielsen, 1969)

Newborns with erythroblastosis exhibited a number of changes in the parameters of coagulation and fibrinolysis.

First phase of coagulation. As compared with normal newborn infants t term the platelet count fell gradually with increasing erythroblastosis. As lready mentioned, the differences were significant only in the severe cases (group 3). This results is in agreement with those reported in the litera-

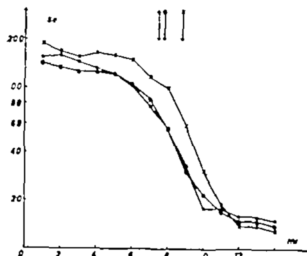


Fig 5 Thromboplastin activation curve of peripheral blood drawn immediately after delivery from 10 women an a erage of five weeks before estimated date of confinement. x—x 10 normal adult women, two-stage TAT ●—● 10 women, two-stage TAT immediately after delivery O—O 10 women, three-stage TAT immediately after delivery

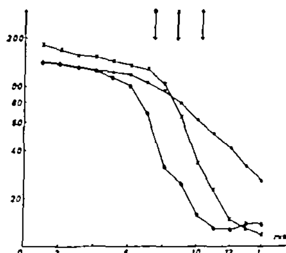


Fig 7 Thromboplastin activation curve of venous cord blood from 10 mildly erythroblastotic infants (group 1). x— 10 normal adult women, two-stage TAT ●—● 10 erythroblastotic infants, two-stage TAT O—O 10 erythroblastotic infants, three-stage TAT

not significant, but accordingly the TAT three stage shows an increased content of clot-promoting components in the plasma, manifested by the rapid course of the curve and the short recalcification time

Comparison of mildly erythroblastotic newborn infants (group 1) with normal newborn infants at term (group 4) showed a significantly reduced PP ($p<0\,001$) and factor V ($0\,01>P>0\,001$) Similarly the fibrinolytic activity was reduced, but this was significant only for iso-electrically precipitated plasma on heated fibrin plates ($p<0\,001$) There was no change in the TAT two-stage apart from a slightly reduced t_1 ($0\,05>p>0\,02$) The TAT three-stage ran a somewhat more rapid course for the erythroblastotic infants, but the recalcification time was of the same magnitude in both groups, so that the content of clot promoting components was largely unchanged.

When, thereafter comparing infants with severe erythroblastosis (groups 3) with normal newborn infants at term (group 4) the author found some of the same changes as in group 1 although

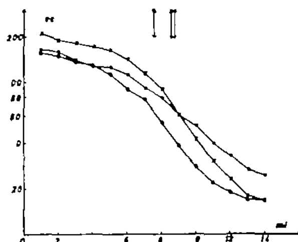


Fig 6 Thromboplastin activation curve of venous cord blood from 20 normal infants. x— 20 normal adult women, two-stage TAT ●—● 20 normal infants, two-stage TAT O—O 20 normal infants, three-stage TAT

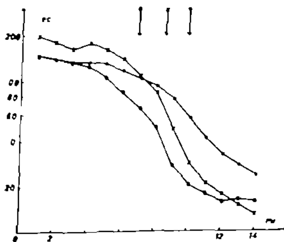


Fig 8 Thromboplastin activation curve of venous cord blood from 15 moderately erythroblastotic infants (group 2). — 14 normal adult women, two-stage TAT; ●—● 15 erythroblastotic infants, two-stage TAT O—O 15 erythroblastotic infants, three-stage TAT

they were more obvious, and a number of new changes: a reduced PP ($p < 0.001$), factor V ($0.01 > p > 0.001$), and platelet count ($p < 0.001$) as well as reduced fibrinolytic activity by all four measuring methods: unprecipitated plasma on standard plates ($0.05 > p > 0.02$), iso-electrically precipitated plasma on standard plates ($0.01 > p > 0.001$), unprecipitated plasma on heated fibrin plates ($0.01 > p > 0.001$) and iso-electrically precipitated plasma on heated fibrin plates ($p < 0.001$). The course of the TAT two-stage had become more rapid, with a shortened t_1 ($0.01 > p > 0.001$) and a tendency to shortened t_T, T_{max}, and recalcification time. The course of the TAT three-stage also showed an increased content of clot promoting components in the plasma.

Since the infants with severe erythroblastosis had a low birth weight (2830 g) and were born, on average 3½ weeks prematurely, they were also compared with normal premature babies (group 5) with an average birth weight of 2260 g and born about 5 weeks before term. This showed the individual parameters of coagulation and fibrinolysis to be in the same range, except for the platelet count which was reduced in the erythroblastotic infants ($0.05 > p > 0.02$). In addition, the course of the TAT two-stage was considerably accelerated in these infants, with significant shortening of t ($0.05 > p > 0.02$), T_{max} ($0.05 > p > 0.02$), t_{max} ($0.05 > p > 0.02$), and recalcification time ($p < 0.001$). In accordance with these findings, the course of the TAT three-stage test indicated a considerably increased content of clot-promoting components in the plasma.



Fig. 10. Thromboplastin activation curve of venous cord blood from 10 premature infants (group 5). — 10 normal adult women, two-stage TAT; ●—● 10 premature infants, two-stage TAT; O—O 10 premature infants, three-stage TAT.

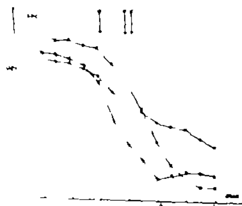


Fig. 9. Thromboplastin activation curve of venous cord blood from 7 severely erythroblastotic infants (group 3). 7 normal adult women, two-stage TAT; ●—● 7 erythroblastotic infants, two-stage TAT; O—O, 7 erythroblastotic infants, three-stage TAT.

DISCUSSION

The results submitted above show that *immunization of pregnant women by Rhesus D antibody* exerts no influence upon the maternal parameters of coagulation or fibrinolysis, not even in the case of massive immunization (group 3). The tendency to premature delivery of Rhesus-immunized mothers may contribute to the reduction in PP (174%) when compared with normal mothers at term (227%), cf. e.g. Nielsen (1969 *d*). Since the PP was calculated by the aid of dilution curves plotted on logarithmic paper, the uncertainty is most marked at high values, and this too may have been contributory.

The content of clot-promoting components in the maternal plasma will not be discussed further here, as the various theories advanced to explain this phenomenon have been discussed in a previous paper (Nielsen 1969 *a*).

Newborns with erythroblastosis exhibited a number of changes in the parameters of coagulation and fibrinolysis.

First phase of coagulation. As compared with normal newborn infants at term the platelet count fell gradually with increasing erythroblastosis. As already mentioned, the differences were significant only in the severe cases (group 3). This results is in agreement with those reported in the litera-

ture. Attempts have been made to explain this decrease in platelet count as a consequence the immunological process, as there may be platelet incompatibility along with erythrocyte incompatibility either in the form of specific platelet antibodies or as a result of the Rhesus D antibody (Stefanini & Dameshek, 1955 Moulinier 1967 and others).

Ekert & Mathew (1967) as mentioned above studied the platelet count and fibrinogen content in erythroblastotic newborn infants. Finding a low platelet count but a normal fibrinogen content, they abandoned the theory that this may be due to intravascular coagulation caused by thromboplastin released from the haemolysed erythrocytes. Instead, they suggested an "isoimmune pathogenesis" as the most likely explanation.

The clot-promoting ability of haemolysed erythrocytes was described as early as 1954 by Quick. The composition of the released substance a phospholipid called erythrocytin has not been fully elucidated. This subject has been reviewed by Mey & Hesse (1966)

The present results concerning TAT two- and three stage show in keeping with the named studies on erythrocytin, that the clot-promoting activity in the plasma of the erythroblastotic infants increases with the severity of the erythroblastosis. Regardless of the normal fibrinogen content it cannot be ruled out that the increased clot promoting activity in the plasma may contribute to the low platelet counts in severe cases of erythroblastosis. However there must be a possibility of relatively modest degrees of intravascular coagulation, as no significant changes in PTT have been demonstrated.

Second phase of coagulation Comparison with normal newborn infants at term showed a significant reduction in PP and factor V for all three groups of erythroblastotic infants, the lowest values being found in group 3 However the differences between the three groups were not significant. The prothrombin time on the other hand, was unchanged. On comparison with a group of normal premature infants (group 5) there was no significant difference between normal premature infants and erythroblastotic infants in respect to PP and factor V Thus, it is reasonable to conclude that mild prematurity in the erythroblastotic infants may have contributed to the demonstrated changes. The Rhesus disease itself however must also be operative as the changes found were of the same magnitude in all three groups of erythroblastotic infants (average birth weight 3380 g, 3080 g, and 2830 g respectively)). The explanation is possibly to be sought in impaired hepatic function in the erythroblastotic infants, causing a reduced synthesis and possibly also a poorer utilization of vitamin K from the mother Slightly increased intravascular coagulation may also be a contributory factor

A direct comparison of the present results with those reported in the literature is not possible, as the time and technique of blood sampling are not identical Moreover several of the reports are based upon only one or a few observations. On the whole, however there seems to be a reduction in the coagulation factors of the second phase in severe cases of erythroblastosis.

Third phase of coagulation Engström & Kager (1961) as well as Ekert & Mathew (1967), as already mentioned, have reported that the fibrinogen content in erythroblastotic newborn infants is in the same range as in normal newborn infants, regardless of the severity of the disease. These results accord precisely with the present ones. In contradistinction, Rice (1953) has reported a case of hypofibrinogenaemia in a premature infant (1900 g) with erythroblastosis, but as pointed out by Engström & Kager this may have been a result of intravascular coagulation due to other causes Nevertheless, it seems reasonable to imagine that severe erythroblastosis *must* be able to produce intravascular coagulation of a considerable degree, cf the effect of erythrocytin.

No effect upon the thrombin time was demonstrated.

Fibrinolysis. As already mentioned, a decreasing fibrinolytic activity was found on a comparison of normal newborn infants at term with mildly erythroblastotic newborn infants (group 1). Comparison of the various groups of erythroblastotic infants showed groups 1 and 2 to be practically identical while in group 3 fibrinolytic activity was reduced, but the difference is not significant.

Several factors may explain the decreasing activity In the first place a steadily decreasing birth weight, the fibrinolytic activity in premature infants being below that of mature infants. This subject has been reviewed int. al. by Nielsen (1969 *d*) In the second place four out of the

seven infants of group 3 were delivered by Caesarean section which often gives rise to a reduced activity in the newborn infant's plasma (cf Nielsen, 1969 *b* 1969 *c*) Lastly the average duration of labour was shorter for erythroblastotic than for full-term infants.

No changes in plasminogen content were demonstrated as a consequence of erythroblastosis.

REFERENCES

de Bruyne, J I & Creveld, S Etud néo-natal 4 149 1955

Dam, J Tage-Hansen, E & Plum, P Ugeskr læg *101* 896, 1939

Ekert, H & Mathew R. Y Med J Aust 2 844, 1967

Engstrom, L & Kaper L. Acta paediat 50 581 1961

Hartmann, J R., Howell, D A & Diamond, L. K.: Amer J Dis Child 90 594 1955

Heyn, R. M., Rosenfeld, I. H Grossman, B. J & Stuart, J D Pediatrics 9 327 1952.

Mey U & Hewe, P Blut *13* 30, 1966.

Moulinier J Nouv Rev franc Hémat 7 443 1967

Nielsen, N. C.: Acta obstet gynec scand 48 371, 1969 *a*.

— Acta obstet gynec scand 48 392, 1969 *b*.

— Acta obstet gynec scand 48 405 1969

— Acta obstet gynec scand 48, 505 1969 *d*.

Quick, A. J Georgatsos, J G & Hussey C. V Amer J med Sci 228 207 1954

Rice, W G J Pediat 42. 231 1953.

Stefanini, M. & Dameshek, W The Hemorrhagic Disorders, Grune & Stratton, New York 1955

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ture Attempts have been made to explain this decrease in platelet count as a consequence the immunological process, as there may be platelet incompatibility along with erythrocyte incompatibility either in the form of specific platelet antibodies or as a result of the Rhesus D antibody (Stefanini & Dameshek, 1955 Moulinier 1967 and others)

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THE INFLUENCE OF EXCHANGE TRANSFUSION UPON COAGULATION AND FIBRINOLYSIS IN NEWBORN INFANTS WITH ERYTHROBLASTOSIS

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Abstract. A comparative study of the factors concerned with coagulation and fibrinolysis in newborn infants with erythroblastosis—(a) at the time of birth, (b) before, and (c) after exchange transfusion—showed the following significant changes:

A. During the period from birth until the start of the exchange transfusion (an average of approximately 5 hours): A decrease in PP and factor V simultaneously with markedly decreasing fibrinolytic activity.

B. During the period from before until after the exchange transfusion: A marked fall in the platelet count, an increase in the PP but a prolonged Quick time. In addition, a slight fall in the fibrinogen content simultaneously with a slight, but not significant, increase in fibrinolytic activity. Moreover, a pronounced increase in plasminogen content.

The cause of these changes is discussed, with particular reference to the levels of factors, in the donor blood, concerned with coagulation and fibrinolysis.

Erythroblastosis gives rise to a number of changes in the newborn infant's coagulation and fibrinolytic systems (see the preceding paper).

It has long been recognized that erythroblastosis may be associated with a haemorrhagic diathesis in the newborn infant. Therefore a number of workers have previously investigated the influence of exchange transfusion upon coagulation in the erythroblastotic infant. However, these studies have usually been concerned merely with individual parameters of coagulation and have not included a complete assessment of coagulation as well as fibrinolysis in these infants.

PREVIOUS INVESTIGATIONS

Previous publications will be reviewed below in relation to the phase or phases of coagulation with which they have been concerned.

First phase of coagulation

Platelets. Several investigations have shown a considerable decrease in the platelet count following exchange transfusion (e.t.). This was observed by Desforges & O'Connell (1955), Krevans & Jackson (1955), Nold (1960), Mollison (1961), Durr et al. (1963), and de Bruijne et al. (1956). True, the last-mentioned authors did not find the decrease immediately after the e.t.

In regard to the other factors included in the first phase of coagulation (factors VIII, IX, XI, and XII) there have been no reports except for a study of the recalcification time which according to Nold (1960) remained unchanged.

Second phase of coagulation

Nold (1960) found an increased content of second-phase factors following e.t. manifested by a shortened Quick time. In accordance with this finding, there was an increased content of factor II (prothrombin) and factor VII (proconvertin), while factor V (proaccelerin) was practically unchanged in twelve cases and greatly reduced in two. In serial analyses during e.t. Bernini Canani et al. (1965) found a slight increase of factor II and a somewhat more marked increase of factor VII, while factor V showed a slight fall.

Third phase of coagulation

Nold (1960) found a slight fall in fibrinogen content following e.t. (200–300 mg/100 ml before and 100–140 mg/100 ml after), but an unchanged antithrombin time. Tóth et al. (1963) on the other hand, demonstrated a highly significant fall in fibrinogen content following e.t.

group 1 *a*, but dra immediately before the hich as performed an average of 4 hours 40 min after birth (range 1 hour 20 min 8 hours 30 min).

(*c*) Blood samples dra immediately after the t. from the same infants, ew disposable plastic catheter being inserted to prevent contamination by possible thrombi at the exchange catheter. The infants were treated ith an average of 395 ml hole blood to which as added citrate (range 300–460 ml) and 120 ml packed blood ith citrate (range 60–160 ml).

Group

T elucidate the parameters of coagulation and fibrinoly sis in the bank blood, analyses ere done also on samples from ten bottles of donor blood hich were not, however used for the preset transfusion. All the transfused blood as freshly drawn, e. less than 24 hours old. In addition, the haematocrit was determined on ten bottles of packed blood dra and average of 2.8 days before use (range 1 5 days). Studies of coagulation or fibrinolysis could not be done on this blood as it contained too little plasma.

Group 3

T evaluate the quality of the bank blood it as compared with blood samples from 25 normal non-pregnant omen. This control series has been described previously (Nielsen, 1969 *a*).

The blood samples from the adults ere drawn from an ante-cubital vein after application of light tourniquet. I the newborn infants the cord as incised close to the skin, and disposable plastic catheter as inserted through the umbilical vein. The samples ere used *only* if there was free flow of blood through the catheter. The technique of the blood sampling and the further treatment of the samples have been described previously. Determination of recalcification time, the thromboplastin

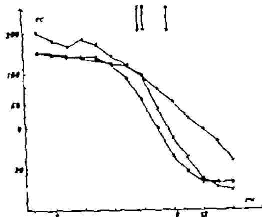


Fig 2. Thromboplastin activation curve of enous cord blood from 10 infants with erythroblastosis dra immediately before exchange transfusion — 9 normal adult women, two-stage TAT ●—● 10 infants with erythroblastosis, two-stage TAT ○—○ 10 infants with erythroblastosis, three-stage TAT

activation test (TAT) two- and three-stage, partial thromboplastin time (PTT), thrombin time, prothrombin time (Quick), factor V prothrombin-proconvertin (PP), fibrinogen content and measurement of fibrinolytic activity in the plasma and in iso-electrically precipitated plasma on unheated fibrin plates (standard plates) and on heated fibrin plates, as well as plasminogen, haematocrit, and platelet counts ere also carried out as described previously (Nielsen, 1969 *a*).



Fig. 1. Thromboplastin activation curve of venous cord blood from 10 infants with erythroblastosis drawn *immediately after delivery* — 9 normal adult women, two-stage TAT ●—● 10 infants ith erythroblastosis, two-stage TAT ○—○ 10 infants ith erythroblastosis, three-stage TAT

RESULTS

The results of the studies of coagulation and fibrinolysis are listed in Table I, while Figs. 1 , and 3 give the results for the TAT and recalcification times.

A comparison of group 1 *a* (erythroblastotic infants at birth) with group 1 *b* (samples from the same infant immediately before the e.t.) gives an impression of the changes in the *parameters f coagulation and fibrinolysis during th first 4 5 hours after birth.* The following significant changes were found. reduction of PP ($0.05 > p \quad 0.02$) and factor V ($0.02 > p > 0.01$) and a reduced fibrinolytic activity by all four measuring methods unprecipitated plasma on standard plates ($0.02 > p > 0.01$), iso-electrically precipitated plasma on standard plates ($0.01 > p > 0.001$), unprecipitated plasma on heated *fibrin plates* ($p < 0.001$), and iso-electrically precipitated plasma on heated fibrin plates ($0.01 > p > 0.001$).

Comparison of group *1 b* (blood samples re-

Table I *Results of coagulation and fibrinolysis studies*

	Erythroblastotic infants									
	Immediately after delivery		*Before exchange transfusion*		*After exchange transfusion*		*Normal bank blood*		Normal adult women (not pregnant)	
Tests, see Methods	x̄ and n	Range est. S.D	x̄ and	Range est. S.D	x̄ and n	Range est. S.D	x̄ and n	Range est. S.D	x̄ and n	Range est S.D
Platelets (thousands per cu. mm)	316 n=10	173–449 ±94	334 n=10	198–500 ±89	162 n=10	78–289 ±54	236 n=10	177–265 ±31	352 =25	223–491 ±77
Proaccelerin (%)	97 n=10	75–120 ±16	81 =10	64–100 ±11	74 n=10	52 105 ±17	86 n=10	67–103 ±12	104 =25	85–145 ±16
Prothrombin time (sec)	18 n=10	16–21 ±1.5	19 n=10	18–21 ±1 0	22 n=10	20–23 ±0 8	20 n=10	18–22 ±1.3	18 n=25	15–21 ±1.2
P and P (%)	61 n=10	43–86 ±13	50 n=10	37–73 ±10	62 n=10	48–73 ±9.3	95 n=10	68–135 ±19	103 n=25	76–120 ±13
Partial thromboplastin time (sec)	90 n=10	83–112 ±8.9	92 =10	82–113 ±8 8	85 =10	82–92 ±3 0	80 n=10	73–85 ±4 6	81 =25	69–100 ±5 9
Thrombin time (sec)	12 n=10	10–18 ±2.1	12 =10	10–14 ±1 1	11 =10	8–13 ±1.5	7 n=10	5–9 ±0.9	9 =25	7 12 ±1.9
Fibrinogen (mg per 100 ml)	244 n=10	155–325 ±53	244 =10	190–305 ±40	206 n=10	150– 45 ±29	255 =10	225–320 ±32	271 =25	185–368 ±45
Haematocrit (%)	48 n=10	41–60 ±6.8	49 n=10	33–60 ±9.3	52 n=10	39–62 ±8 0	42 =10	36–52 ±5.0	40 =25	34–46 ±3 1
Haematocrit, packed blood (%)							86 =10	74–93 ±6.5		
Untreated fibrin plates untreated plasma (sq mm)	26 n=10	0–81 ±25	1 n=10	0–16 ±3 4	8 n=10	0–49 ±18	0 =10	0 ±0	0 =25	0 ±0
Untreated fibrin plates, Euglobulins (sq. mm)	165 =10	29–440 ±125	16 n=10	0–36 ±14	81 n=9	0–355 ±119	22 n=10	0–49 ±19	12 n=25	0–36 ±10
Heated fibrin plates, untreated plasma (sq. mm)	14 =10	0–25 ±11	0 n=10	0 ±0	7 n=10	0–49 ±16	0 n=10	0 ±0	0 n 25	0 ±0
Heated fibrin plates, Euglobulins (sq mm)	27 =10	14–36 ±7 0	9 n=10	0–25 ±9 0	21 =9	0–64 ±22	10 n=10	0–22 ±8 7	12 =25	0–32 ±8.0
Plasminogen (μg Cu-Tyrosine per ml)	64 n=10	54–78 ±8 6	60 =10	36–80 ±13	98 =10	73–117 ±17	133 =10	110–177 ±22	127 =25	78–172 ±23

x̄ = arithmetic average   n = number of estimations.
Range = range of individual results (x)   est. S.D = estimated standard deviations. $\pm\sqrt{\Sigma(x-\bar{x})^2/(n-1)}$.

Fibrinolysis. There have been no reports on fibrinolytic activity before and after e t.

MATERIAL AND METHODS

The present analyses are based pon blood samples from the following three groups:

Group 1

(*a*) Blood samples drawn not later than 20 mi after birth from 10 infants with erythroblastosis due to Rhesus D antibody (in three cases C+D and I one case D+E). Labour had been induced by intranasal oxytocin followed by rupture *of the membranes or merely by rupturing* the membranes. The infants ere born, on a erage 4 weeks before term (range 1–4 weeks) and their a erage birth weight was 2900 g (range 2100–3820 g). At the time of birth the direct Coombs test was positive (in one case moderately and in the remainde ery strongly so). Frequently moderate anaemia was present haematocrit averaging 48% (range 41–60%). All the mothers had received vitamin K before delivery in dosage as described previously (Nielsen, 1969). Immediately after birth, but before the blood samples were taken, all the infants received itamin K in the form f menadione, 1 mg i.m.

The infants included in the study from part of a previously published series (Nielsen, 1969).

(*b*) Blood samples from the same ten infants as in

fter the third day. Similarly the Quick time was significantly prolonged at this time. These results confirm a number of earlier reports that the Quick time gets prolonged in bank blood after a few days (Rhoads & Panzer 1939; Quick, 1940; Reinhold et al., 1940; Ziegler et al. 1940). The bank blood used by us showed almost the same changes, only the alterations in factor V and in the Quick time were already present after 24 hours. Seegers & Schneider (1951) on the other hand, found an unchanged prothrombin for the first 20 days, and factor V was not reduced until fter five days.

As is apparent from Table I, a normal fibrinogen content was found in the donor blood. This also confirms Gerhartz & Blum's study.

By the present methods no changes were found in fibrinolytic activity or in the plasminogen content of this blood after 24 hours.

All the changes in the parameters of coagulation and fibrinolysis *caused by the exchange transfusion* may be explained on the basis of the composition of the donor blood. The e.t. consisted, as already mentioned, of 395 ml whole blood and 170 ml packed blood. As the packed blood was older, averaging 2.8 days, it might be expected to have had a lower platelet count and lower content of coagulation factors than ordinary donor blood which has not been standing for more than 24 hours.

First phase of coagulation. The pronounced fall in the platelet count compared with the findings before the e.t. is in accordance with the results reported in the literature. The explanation must be that the donor blood has a lower platelet count than the infant's blood. The reason why a fall to below the level of the donor blood occurs may be that the platelet count in packed blood is even lower. It might be imagined that increased intravascular coagulation during the exchange was contributory, but this cannot have been so as the TAT three-stage does not show signs of increased activity after the e.t.

The PTT and recalcification time determination in TAT two-stage demonstrated a slightly increased, but not significant, in the firstphase factors. These shifts may also be explained as a result of the donor blood PTT.

Second phase of coagulation. After the e.t. a significant increase in the PP had occurred, while the labile factor V was still decreasing, and this may be the explanation why the Quick time was prolonged. The prolonged Quick time in the donor blood may also be contributory. The long Quick time is at variance with Nold's study which showed a shortening after the e.t. in spite of the fact that the factor V content was lower in the donor blood than in the infant blood prior to the e.t., while factor II and factor VII were in the same range.

The demonstrated increase in PP was also manifest in the TAT two-stage, the latter part of the curve running a more rapid course after than before the e.t.

Third phase of coagulation. The slight decrease in fibrinogen ($0.05 > p > 0.02$) after the e.t. cannot be explained directly as a consequence of the fibrinogen content in the donor blood, as this was higher than in the infant blood, before as well as after the e.t. The explanation cannot either be found in the composition of the packed blood, since the fibrinogen content, as demonstrated by Gerhartz & Blum (1965) remains unchanged during the first 10 days after collection. Tóth et al. (1963) have reported a pronounced fall in fibrinogen after e.t. which in their opinion may have been due to acute defibrination. This explanation cannot be accepted in the present cases, as the TAT three-stage did not show signs of increased activation after the e.t. As is apparent from what is stated below that increased fibrinolysis may have been responsible.

Fibrinolysis. Barrie (1965), Boda et al. (1966), and others have demonstrated that an increased metabolic acidosis occurs following e.t. with citrated blood. Since increased acidosis gives rise to increasing fibrinolytic activity (Engström & Kager 1964 *b*), the acidosis is presumably responsible for the mild, non-significant, increase demonstrated after the e.t.

The greatly increased plasminogen content after e.t. must be related to the high plasminogen content of the donor blood.

REFERENCES

Astrup, T. & Albrechtsen, O. K.: Thrombos. Diathes. haemorrh. (Stuttg.) 21, 117, 1969.

Barrie, H.: Lancet 2, 712, 1965.

Bellet, F. K.: Rev. belge Path. 24, 422, 1955.

Berta Casaal, M., Rea, F. & Cirpano, D. A.: Boll. Soc. ital. Biol. sper. 41, 895, 1965.

Boda, D., Tóth, G. Y., Murányi, L. & Eck, E.: Acta paediat. 55, 217, 1966.

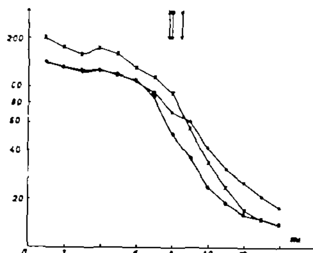


Fig 3 Thromboplastin activation curve of venous cord blood from 10 infants with erythroblastosis drawn immediately after exchange transfusion. × — 9 normal adult women, two-stage TAT ●—● 10 infants with erythroblastosis, two-stage TAT ○—○ 10 infants with erythroblastosis, three-stage TAT

moved immediately before the e.t.) with group I *c* (blood samples from the same infants after the e t.) illustrates *the influence of the exchange transfusion upon coagulation and fibrinolysis* After the e.t. the following significant changes were found, a prolonged Quick time ($p < 0\ 001$) and increased PP ($0\ 02 > p > 0\ 01$) reduced fibrinogen content ($0\ 05 > p > 0\ 02$) and a marked fall in platelet count ($p < 0\ 001$) As far as fibrinolysis is concerned, no significant changes were demonstrated apart from an increased plasminogen content ($p < 0\ 001$)

Lastly *the parameters of coagulation and fibrinolysis in the bank blood* (group 2) were evaluated by comparing it with blood from normal, non pregnant women (group 3) This showed the following significant changes in the bank blood, a prolonged Quick time ($p < 0\ 001$) reduced factor V ($p < 0\ 001$) reduced thrombin time ($p < 0\ 001$) and reduced platelet count ($p < 0\ 001$) but no differences in fibrinolytic activity

DISCUSSION

It has been pointed out by Beller (1955) as well as by Vest & Meier (1957) and others that the content of factors II V and VII decreases in normal newborn infants during the first few hours after birth. As in apparent from Table I the same applies to erythroblastotic newborn infants. In other words, this is a physiological phenomenon, not a change due to the maternal Rhesus immunization. Incidentally no changes in *coagulation factors* have been demonstrated within the first hours of life apart from a slight flattening of the latter part of the curve in the TAT two-stage which may be explained by the reduction of the named factors. TAT three-stage shows a decreasing clot-promoting activity in groups 1 *b* compared with the findings at birth The explanation is probably that the effect of Wessler s serum thrombotic accelerator which presumably causes the increased clot-promoting activity (cf Nielsen 1969 *a*) subsides in the course of a few hours (Wessler 1955 and Astrup & Albrechtsen 1969)

Changes in *fibrinolytic activity* after birth in normal newborn infants have been reported by Engström & Kager (1964 *a*) who demonstrated that the highly increased activity at the time of birth will return to normal in a few hours. This observation is explained by changes in the blood gases and acid-base balance which take place at this time. The present cases show a similar return to normal of fibrinolytic activity in erythroblastotic newborn infants during the first few hours after birth.

As already mentioned, the influence of the e.t. upon the factors concerned with coagulation and fibrinolysis can only be assessed when the *donor blood* has also been analysed. Although silicon coated vessels were used for storing this blood, a significant reduction in platelet count was found in blood drawn in maximum of 24 hours previously This finding confirms previous studies, especially those of Nold (1960) who plotted a curve illustrating the average fall in the platelet count in 50 bottles of donor blood over a period of 17 days. This curve shows a fairly marked reduction from day to day in the first week. The explanation is presumably a consumption phenomenon induced by microcoagulation through activation of the contact factors in spite of the technique of drawing and storing the blood using silicon treated apparatus.

The factor VIII content is normal during the first 24 hours (Revol et al. 1965) in keeping with the unchanged PTT in the present study

Gerhartz & Blum (1965) found a normal level of factors II V and VII in blood after 24 hours storage while factor V was significantly reduced

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COAGULATION AND FIBRINOLYSIS IN MOTHERS AND THEIR NEWBORN INFANTS FOLLOWING PREMATURE SEPARATION OF THE PLACENTA

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Abstract. Investigation of the parameters of coagulation and fibrinolysis in mothers with premature separation of the placenta (P.S.P.) and their newborn infants, compared with normal prematurely delivered women and their normal premature infants, showed the following:

A. *In the mothers.* With increasing severity of the premature separation also increasing alteration in the parameters of coagulation i.e. decreasing platelet count, factor V, prothrombin-proconvertin, fibrinogen content, and prolonged partial thromboplastin time. In severe cases the TAT three-stage indicated slightly increased content of coagulation-activating components in the plasma.

No definite effect upon fibrinolytic activity of premature separation of the placenta.

B. *In the infants.* In premature separation of the placenta, the infants also exhibited changes in their coagulation status, most distinct in the most severe cases. These changes consisted of decreasing platelet counts, factor V, prothrombin-proconvertin, fibrinogen content, and prolonged partial thromboplastin time. For platelet count and fibrinogen the changes were not significant. As for the mothers the TAT three-stage showed an increased content of clot-promoting components in the plasma in the most severe cases.

No definite effect of premature separation of the placenta upon fibrinolytic activity could be shown.

The cause of the demonstrated changes is discussed and therapeutic possibilities mentioned.

Alterations in maternal coagulation and fibrinolysis in premature separation of the normally implanted placenta (P.S.P.) have been described many times, both in the form of individual case reports and large series.

During the past few years there have moreover been a few reports on P.S.P. giving rise to alterations in the parameters of coagulation and fibrinolysis in the newborn infants.

The object of the present paper is to submit a systematic study of a number of mothers having P.S.P. of varying severity and their newborn infants to elucidate whether, apart from the known alterations in the maternal blood, P.S.P. may also influence coagulation and fibrinolysis in the newborn infants.

PREVIOUS INVESTIGATIONS

Numerous studies on coagulation and fibrinolysis in mothers with P.S.P. have been reported. The literature was reviewed by Nilsen (1958, 1963) who also submitted a large series of his own.

On the other hand, only a few studies have been concerned with the influence of P.S.P. upon coagulation and fibrinolysis in the newborn infant. Valentine (1958) reported a case of P.S.P. with Couvelaire uterus in which investigations 24 hours after delivery revealed highly increased fibrinolytic activity in the mother as well as the infant.

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Engström, L. & Kager L. Acta paediat 53 376, 1964 a
— Acta paediat 53 329 1964 b
Gerhartz, H & Blum, K. U. Bibl haemat 3 1.35 1965
Krevans, J R. & Jackson, D P J Amer med Ass 159 171 1955
Mollison, P L. Blood Transfusion in Clinical Medicine, Blackwell Scientific Publ., Oxford, 1961
Nielsen, N C Acta obstet gynec scand 48 371 1969 a.
— Acta obstet gynec scand 48 523 1969 c
Nold, B Folia haemat (Frankfurt) 4 325 1960.
Quick, A. J J Amer med Ass 114 134., 1940.
Reinbold, J Valentine E. H. & Ferguson, L. K. Amer J Med Sci 199 744, 1940
Revol, L., Belleville, J Thouverez, P & Denhaut, M. G Bibl haemat .3 1700, 1965
Rhoads, J E. & Panzer L. M. J Amer med Ass 112 309 1939
Seegers, W H. & Schneider C. L. Amer J Obstet Gynec 61 A Suppl 469 1951
Tóth, G Virág, I & Ordögh, B Z Kinderheilk 89 22., 1964
Vest, M & Meir W Ann paediat 189 282, 1957
Wessler S. J clin Invest 34 647 1955
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COAGULATION AND FIBRINOLYSIS IN MOTHERS AND THEIR NEWBORN INFANTS FOLLOWING PREMATURE SEPARATION OF THE PLACENTA

Niels Chr. Nielsen

From the University Maternity Hospital (Head: Professor M. Ingerslev), Århus, Denmark

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A. *In the mothers.* With increasing severity of the premature separation also increasing alteration in the parameters of coagulation: decreasing platelet count, factor V, prothrombin-proconvertin, fibrinogen content, and prolonged partial thromboplastin time. In severe cases the TAT three-stage indicated a slightly increased content of coagulation-activating components in the plasma.

No definite effect upon fibrinolytic activity of premature separation of the placenta.

B. *In the infants.* In premature separation of the placenta, the infants also exhibited changes in their coagulation status, most distinct in the most severe cases. These changes consisted of decreasing platelet counts, factor V, prothrombin-proconvertin, fibrinogen content, and prolonged partial thromboplastin time. For platelet count and fibrinogen the changes were not significant. As for the mothers the TAT three-stage showed an increased content of clot-promoting components in the plasma in the most severe cases.

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The cause of the demonstrated changes is discussed and therapeutic possibilities mentioned.

Alterations in maternal coagulation and fibrinolysis in premature separation of the normally implanted placenta (P.S.P.) have been described many times, both in the form of individual case reports and large series.

During the past few years there have, moreover, been   few reports on P.S.P. giving rise to alterations in the parameters of coagulation and fibrinolysis in the newborn infants.

The object of the present paper is to submit a systematic study of a   number of mothers having P.S.P. of varying severity and their newborn infants to elucidate whether, apart from the known alterations in the maternal blood, P.S.P. may also influence coagulation and fibrinolysis in the newborn infants.

PREVIOUS INVESTIGATIONS

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— Acta paediat 53 329 1964 b
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— Acta obstet gynec scand 48 523 1969 c
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Tóth, G Virág, I. & Ördögh, B. Z Kinderheilk 89 222, 1964
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— Acta paediat *53* 329 1964 *b*
Gerhartz, H. & Blum, K.-U Bibl haemat *23* 1235 1965
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— Acta obstet gynec scand *48* 523 1969
Nold, B Folia haemat (Frankfurt) *4* 3-5 1960.
Quick, A. J J Amer med Ass *114* 1342, 1940
Reinhold, J Valentine E. H. & Ferguson, L. K. Amer J Med Sci *199* 744 1940
Revol, L., Belleville, J Thouverez, P & Denhaut, M. G. Bibl haemat *23* 1200, 1965
Rhoads, J E. & Panzer L. M., J Amer med Ass *112* 309 1939
Seegers, W H & Schneider C. L. Amer J Obstet Gynec *61 A* Suppl 469 1951
Tóth, G., Virág, L & Ordögh, B. Z Kinderheilk *89* 222, 1964
Vest, M. & Meir W Ann paediat *189* 482, 1957
Wexler S. J clin Invest *34* 647 1955
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Table I. *Results of studies of coagulation and fibrinolysis in normal women and in women with premature separation of the placenta*

Tests, see Methods	Normal women premature delivery		Women with P.S.P			
			First degree		Second degree	
	x̄ and n	Range est. S.D	x̄ and n	Range est. S.D	x̄ and n	Range est. S.D
Platelets (thousands per cu. mm)	223 20	139–440 ±65	160 9	76–218 ±43	138 5	100–169 ±29
Proaccelerin ( )	106 20	75–135 ±16	105 9	69–160 ±26	70 5	41–83 ±17
Prothrombin time (sec)	18 20	15–20 ±1.3	18 9	16–21 ±1.1	18 5	13–22 ±2.0
P and P ( )	172 20	115–245 ±35	158 9	115–230 ±34	100 5	54–125 ±27
Partial thromboplastin time (sec)	75 20	67–85 ±4.3	77 9	71–82 ±3.8	80 5	76–89 ±5.3
Thrombin time (sec)	6 20	5–8 ±1.1	7 9	5–10 ±1.5	8 5	6–12 ±2.3
Fibrinogen (mg per 100 ml)	517 20	390–730 ±83	431 9	285–570 ±98	299 5	190–415 ±86
Haematocrit ( )	42 20	35–55 ±4.4	40 9	31–47 ±5.2	33 5	30–34 ±1.6
Standard fibrin plates, untreated plasma (sq. mm)	0 20	0 ±0	0 9	0 ±0	0 5	0 ±0
Standard fibrin plates, Euglobulins (sq. mm)	25 20	0–93 ±27	13 9	0–33 ±12	7 5	0–12 ±4.7
Heated fibrin plates, untreated plasma (sq. mm)	0 20	0 ±0	0 9	0 ±0	0 5	0 ±0
Heated fibrin plates, Euglobulins (sq. mm)	18 20	0–49 ±14	15 9	0–56 ±18	6 5	0–23 ±11
Plasminogen (µg Cu-Tyrosine per ml)	172 20	125–230 ±23	166 9	114–200 ±28	170 5	151–189 ±14

x̄ arithmetic average, n number of estimations.
Range = range of individual results (x), est. S.D = estimated standard deviation $\pm\sqrt{\Sigma(x-\bar{x})^2/(n-1)}$.

of the blood sampling and the further processing of the samples has been described previously. Determination of the recalcification time, thromboplastin activation test (TAT) two- and three-stage, partial thromboplastin time (PTT) thrombin time, prothrombin time (Quick), factor V prothrombin proconvertin (PP), fibrinogen content and measurement of fibrinolytic activity in the plasma and in an electrically precipitated plasma on untreated fibrin plates (standard plates) and on heated fibrin plates, as well as plasminogen, haematocrit, and platelet counts were also performed as described previously (Nielsen, 1969).

RESULTS

The results of the studies of *coagulation and fibrinolysis* are given in Tables I and II, those for the TAT and recalcification times in Figs. 1, 2, 3, 4, 5 and 6.

Comparison of normal prematurely delivered women and their infants (group 3) with mothers having P.S.P. grade 1 (mild cases) and their infants (group 1) showed the following significant differences:

A. *Peripheral maternal blood.* Reduced platelet count (0.05 > p > 0.02) and reduced fibrinogen content (0.05 > p > 0.02) in mothers with P.S.P. The TAT two-stage exhibited no major differences between the two groups, and TAT three-stage demonstrated coagulation-activating components of the same magnitude in the plasma from both

tioned that his normal values were derived mainly from the studies of other workers, and that he does not state these three infants birth weights which are important in assessing neonatal coagulation status (Nielsen, 1969 *d*).

In 1968 two cases were reported which indicated the likelihood that P.S.P may cause intravascular coagulation in the infant as well as the mother

Edson et al. (1958) described a case of P.S.P with reduced fibrinogen (194 mg/100 ml) in the maternal blood. No other analyses were mentioned. On the other hand, a number of changes were demonstrated in the infant: Unmeasurable fibrinogen essentially unmeasurable prothrombin and proaccelerin as well as a low content of factor X. Studies for fibrinolysis were not done. The analyses were based on blood samples drawn through a catheter in the umbilical vein 12 hours after birth at which stage the infant exhibited signs of hyaline membrane disease and a haemorrhagic diathesis. The infant was treated with exchange transfusion and fibrinogen but died just over 24 hours after birth. Autopsy revealed mild subdural and severe subarachnoid, intracerebral and intraventricular haemorrhage. Furthermore, microscopic haemorrhage was found in the pancreas and kidneys. The authors concluded that there was intravascular coagulation in mother as well as infant.

Stark et al (1968) described a case of P.S.P 7–8 weeks before term, resulting in the delivery by Caesarean section, of a premature infant, weighing 2040 g. No analyses on maternal blood were mentioned, but the findings in the infant 1½ hours after birth were Fibrinogen 145 mg/100 ml prothrombin 18 % proaccelerin 45 % partial thromboplastin time 97 sec, and pH 7.30 These changes were interpreted as sequelae to intravascular coagulation caused by tissue thromboplastin of placental origin infused into the foetal circulation at the time of the P.S.P The infant was treated with $NaHCO_3$ and heparin. Repeated investigation 80 hours after birth showed fibrinogen to be 185 mg/100 ml prothrombin 45 and proaccelerin 85

MATERIAL AND METHODS

The analyses were performed on blood samples from the following three groups:

Group 1

Nine women with P.S.P grade 1 meaning mild cases of P.S.P with no or little increase in uterine tone, only slight pain, mainly revealed haemorrhage mother unaffected and infant nearly always unaffected. The diagnosis was confirmed by inspection of the placenta. One pregnancy was complicated by chronic pyelonephritis with hypertension and proteinuria, while the others had been uncomplicated until the P.S.P occurred. One patient ga e birth to twins with a common placenta and vascular anastomoses. In four cases prophylactic vitamin K was administered in a dosage as described previously (Nielsen, 1968 *a*) The time of delivery was, on average, 4 wks before term (range 3–9 weeks). One patient was delivered by caesarean section. The maternal blood samples were drawn within the first 25 min after delivery

Blood samples were drawn also from these mothers 10 newborn infants within the first 15 min after birth. The birth weight averaged 7005 g (range 1560–2940 g). One infant died at the age of 7 days. Post mortem diagnoses: Prematurity almost total atelectasis of the lungs. Apart from the prematurity the others showed no abnormalities during their stay in the department

Group

Five women with P.S.P grade , meaning severe cases of P.S.P manifesting itself by sudden, usually severe pain, increased tone of the uterus, and anaemia, partly concealed haemorrhage mother often ill, infant distressed. The diagnosis was confirmed by inspection of the placenta. All the pregnancies had been uncomplicated until the P.S.P occurred. No patient had received prophylactic vitamin K before delivery The time of delivery averaged 4 8 weeks before term (range -8 weeks). Three patients were delivered by Caesarean section. The maternal blood samples were drawn within the first 25 min after delivery and invariably before blood transfusion, if any

Blood samples were drawn also from these patients *five infants* within the first 15 min after birth, The birth weight a eraged 345 g (range 1160–3060 g). Tw infants died within 4 hours of birth. Post mortem diagnoses: Prematurity pulmonary atelectasis, and in one case intraventricular *haemorrhage* and ecchymosis of the pericardium and pleura. Apart from the prematurity the other infants showed no abnormalities while in the department.

Group 3

As a control, we ha group of 20 women delivered prematurely on average, 5.6 weeks before term (range 4–8 weeks) whose pregnancy delivery and puerperium were otherwise normal. Half these mothers had received prophylactic vitamin K before delivery

In addition, these patients 20 premature infants, weighing at birth, on erage, 2020 g (range 1440– 440 g). The control series has been described previously (Nielsen, 1969 *d*).

The maternal blood samples were drawn from an ante-cubital ein after the application of light tourniquet. In the infants the cord was incised close to the skin, and a disposable plastic catheter was introduced through the umbilical ein The samples were used only if there was a free flow of blood through the catheter The technique



Fig. 1. Thromboplastin activation curve of peripheral blood drawn immediately after delivery from 20 women, an average of five weeks before estimated date of confinement. — 19 normal adult women, two-stage TAT ●—● 20 women, two-stage TAT immediately after delivery O—O 20 women, three-stage TAT immediately after delivery

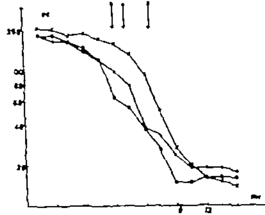


Fig. 3. Thromboplastin activation curve of peripheral blood drawn immediately after delivery from five women with P.S.P of second degree. — 5 normal adult women, two-stage TAT ●—● 5 women with P.S.P two-stage TAT O—O 5 women with P.S.P three-stage TAT

No changes in fibrinolytic activity or in plasminogen apart from reduced activity in iso-electrically precipitated plasma on standard plates (0.02 > p > 0.01) in the newborn infants of mothers with P.S.P

DISCUSSION

The present series includes studies of mothers and their newborn infants in cases where the delivery was complicated by mild or moderately severe P.S.P (grade 1 and grade 2). It is not possible to submit corresponding studies of P.S.P grade 3 (with maternal shock and clinical coagulation disturbances). In these cases the infants were either stillborn or so severely affected that it was not justifiable to remove the blood samples needed for the analyses.

Mothers with P.S.P grade 1 showed a slight reduction of the platelet count and fibrinogen content. In P.S.P grade 2 the changes were more

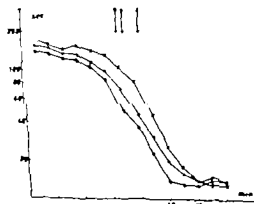


Fig. 2. Thromboplastin activation curve of peripheral blood drawn immediately after delivery from nine women with P.S.P of first degree. — 9 normal adult women, two-stage TAT ●—● 9 women with P.S.P two-stage TAT O—O 9 women with P.S.P three-stage TAT

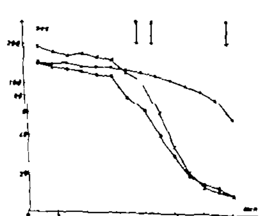


Fig. 4. Thromboplastin activation curve of venous cord blood from 20 premature infants. — 19 normal adult women, two-stage TAT ●—● 20 premature infants, two-stage TAT; O—O 20 premature infants, three-stage TAT

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Table II *Results of studies of coagulation and fibrinolysis in normal premature infants and in infants of mothers with premature separation of the placenta*

	Normal premature infants		Infants of mothers with P.S.P			
			First degree		Second degree	
	$\bar{x}$ and n	Range est. S.D	$\bar{x}$ and n	Range est. S.D	$\bar{x}$ and n	Range est. S.D.
Platelets (thousands per cu. mm)	301 $n=$[illegible]	174–6[illegible] ±109	251 $n=10$	[illegible]–34[illegible] ±74	261 $n=5$	199–356 ±74
Proaccelerin ( )	88 $n=20$	34–150 ±[illegible]7	80 $n=10$	40–1[illegible]0 ±27	51 $n=5$	[illegible]–70 ±13
Prothrombin time (sec)	20 $n=20$	17–[illegible]4 ±[illegible]3	[illegible]0 $n=10$	15–25 ±[illegible]6	22 $n=5$	19–[illegible]7 ±[illegible]7
P and P ( )	41 $n=20$	[illegible]3–78 ±14	39 $n=10$	[illegible]4–60 ±9.9	7 $n=5$	1–[illegible] ±9.2
Partial thromboplastine (sec)	1[illegible]7 $n=20$	97–1[illegible] ±29	128 $n=10$	80–193 ±37	175 $n=5$	101–[illegible]4 ±61
Thrombin time (sec)	12 $n=20$	7–[illegible]4 ±3.9	13 $n=10$	9–18 ±3[illegible]	13 $n=5$	8–17 ±3.5
Fibrinogen (mg per 100 ml)	[illegible]43 $n=$[illegible]0	140–370 > ±75	228 $n=10$	1[illegible]0–385 ±76	190 $n=5$	135–[illegible]35 ±38
Haematocrit (%)	56 $n=$[illegible]0	47–65 ±4.7	56 $n=10$	49–66 ±4.7	50 $n=5$	44–54 ±4.0
Standard fibrin plates, untreated plasma (sq. mm)	45 $n=$[illegible]0	0–70 ±[illegible]	64 $n=10$	9–144 ±5[illegible]	[illegible]6 $n=5$	0–64 ±27
Standard fibrin plates, Euglobulins (sq. mm)	10 $n=20$	[illegible]5–391 ±99	[illegible]35 $n=10$	58–[illegible]0 ±111	84 $n=5$	0–169 ±73
Heated fibrin plates, untreated plasma (sq. mm)	1 $n=20$	0–[illegible]5 ±7.1	14 $n=10$	0–[illegible]8 ±11	9 $n=5$	0–36 ±15
Heated fibrin plates, Euglobulins (sq. mm)	[illegible]6 $n=20$	1–49 ±9.3	[illegible]3 $n=10$	1–36 ±1	16 $n=5$	0–25 ±10
Plasminogen (µg Cu-Tyrosine per ml)	35 $n=$[illegible]0	8–65 ±14	38 $n=10$	19–66 ±14	51 $n=5$	[illegible]279 ±22

See footnote to Table I

groups. No significant changes in fibrinolytic activity

B. *Cord blood* No difference, either in the parameters of coagulation or of fibrinolysis.

Thereafter a comparison of the same normal *prematurely delivered mothers and their infants* (group 3) with mothers having P.S.P grade 2 (severe cases) and their infants (group 2) revealed the following significant differences.

A. *Peripheral maternal blood* In mothers with P.S.P reduced platelet counts ($0.01 > p > 0.001$), PP ($p < 0.001$) factor V ($p < 0.001$) and fibrinogen ($p < 0.001$) with prolonged PTT ($0.05 > p > 0.0$[illegible]) No significant changes in TAT two-stage but possibly a somewhat greater activation in the TAT three-stage. Reduced haematocrit ($p < 0.001$). No significant changes in fibrinolytic activity or plasminogen content except in *isoelectrically precipitated plasma on standard plates* and on heated fibrin plates where the activity was reduced in mothers with P.S.P ($0.01 > p > 0.001$) and ($p < 0.001$).

B *Cord blood.* In newborn infants of mothers with P.S.P reduced PP ($0.05 > p > 0.0$[illegible]) and factor V ($0.01 > p > 0.001$), prolonged PTT (0.0[illegible]$ > p > 0.01$) and reduced haematocrit (0.0[illegible]$ > p > 0.01$) *In addition a non-significant reduction* of the platelet count and of fibrinogen. The course of the TAT two-stage and three stage indicated a slightly increased content of coagulation-activating components in the plasma of the newborn infants *of mothers with P.S.P., but no significant changes.*

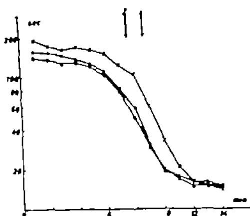


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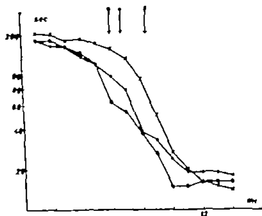


Fig. 3 Thromboplastin activation curve of peripheral blood drawn immediately after delivery from five women with P.S.P of second degree. — 5 normal adult women, two-stage TAT; ●—● 5 women with P.S.P two-stage TAT; ○—○ 5 women with P.S.P three-stage TAT

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DISCUSSION

The present series includes studies of mothers and their newborn infants in cases where the delivery was complicated by mild or moderately severe P.S.P (grade 1 and grade 2). It is not possible to submit corresponding studies of P.S.P grade 3 (with maternal shock and clinical coagulation disturbances). In these cases the infants were either stillborn or so severely affected that it was not justifiable to remove the blood samples needed for the analyses.

Mothers with P.S.P grade 1 showed a slight reduction of the platelet count and fibrinogen content. In P.S.P grade 2 the changes were more

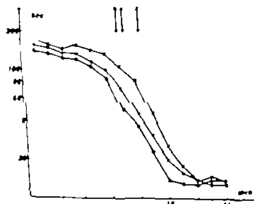


Fig Thromboplastin activation curve of peripheral blood drawn immediately after delivery from nine women with P.S.P of first degree. — 9 normal adult women, two-stage TAT ●—● 9 women with P.S.P two-stage TAT ○—○ 9 women with P.S.P three-stage TAT

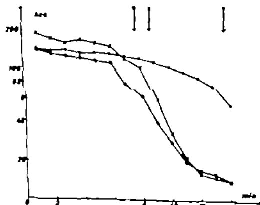


Fig 4 Thromboplastin activation curve of venous cord blood from 20 premature infants. — 19 normal adult women, two-stage TAT ●—● 20 premature infants, two-stage TAT ○—○, 20 premature infants, three-stage TAT

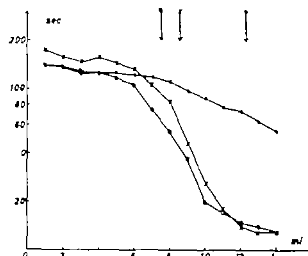


Fig 5 Thromboplastin activation curve of venous cord blood from 10 infants of mothers with P.S.P of first degree. ×—× 9 normal adult women, two-stage TAT ●—● 10 infants of mothers with P.S.P two-stage TAT ○—○ 10 infants of mothers with P.S.P three-stage TAT

pronounced, and included also a reduction of factor V PP and haematocrit and a prolongation of the PTT These changes may be due to mild intravascular coagulation, although the course of the TAT three-stage for P.S.P grade 1 does not suggest this. In P.S.P grade 2 the course of TAT three-stage is compatible with slightly increased clot promoting activity in the plasma. The cause of this activation may be tissue thromboplastin

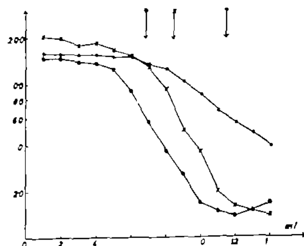


Fig 6 Thromboplastin activation curve f enous cord blood from five infants f mothers with P.S.P of second degree — 5 normal adult women, two-stage TAT ●—● 5 infants f mothers with P.S.P two-stage TAT ○—○ 5 infants of mothers with P S.P three-stage TAT

from the placenta or serum which is released from intravascular coagulation or from the retroplacental clot. In a study on clot-promoting components in circulating blood in a case of abruptio placentae with afigrinogenaemia Skjødt (1967) demonstrated the likelihood of a serum effect. This is in keeping with an experimental study by Astrup & Albrechtsen (1969) who demonstrated that tissue thromboplastin injected into the femoral vein of rabbits gives rise to intravascular coagulation locally while gross clots were never observed in the arterial circulation In no case could they demonstrate tissue thromboplastin in blood drawn from the carotid artery after injection of tissue thromboplastin into the femoral vein. By TAT they could demonstrate a faint, short-lasting clot promoting activity in the arterial blood which they attributed to a serum effect. After intravenous injection of serum, on the other hand, they could demonstrate a distinctly increased activation of coagulation during a period of up to two hours. The conclusion of their study was that tissue thromboplastin injected intravenously is removed from the blood during its passage from the femoral vein to the arterial circulation, probably in the pulmonary capillaries, and that hyper coagulability appears to be caused by a serum effect or by partial activation of the intrinsic coagulation system

Thus, the reduction of the individual coagulation factors demonstrated in the present study may be due to consumption through the formation of an intravascular or retroplacental clot, moreover the haemodilution caused by the haemorrhage may have been operative. On the other hand, fibrinolysis may be ruled out in the present series (cf Table I)

The question is now whether these changes in maternal coagulation and fibrinolysis, caused by P.S.P are demonstrable also in the infants blood.

In the infants of mothers having P S.P grade 1 there were not, as already mentioned, any changes in coagulation or fibrinolysis.

It is different with P S.P grade 2 In spite of the absence of clinical symptoms, the mothers exhibited a number of changes in the coagulation factors which occurred also in their newborn infants, but in a less pronounced degree In the infants too the cause is probably consumption due to mild intravascular coagulation caused by tissue thromboplastin from the placenta. The

slightly increased content of clot-promoting components in the plasma, demonstrated by the TAT three-stage, is then explicable on the background of a serum factor released from the intravascular clot.

Histological examination (Professor K. Nielsen) of preparations from the lungs, spleen, liver pancreas, and kidneys of the two dead infants of mothers having P.S.P grade 2 did not show intravascular fibrin thrombi. Indeed, as is apparent from Table II, there was not much reduction in the fibrinogen content.

The less pronounced fibrinolytic activity in the infants of mothers with P.S.P grade 2 is possibly due to the fact that three of the five infants were delivered by Caesarean section which ppears to ha e a less activating effect than vaginal delivery upon fibrinolysis (Nielsen, 1968 *b*).

Comparison of the results for infants of group 1 2, and 3 confirms a gradual reduction in the content of coagulation factors with increasing severity f the P.S.P These findings, when considering also the two cases reported by Edson et al. (1968) and by Stark et al. (1968), demonstrate that if these infants show signs of a haemorrhagic diathesis, studies of coagulation and fibrinolysis should be carried out with view to treatment, possibly exchange transfusion.

REFERENCES

Astrup, T & Albrechtsen, O. K. Thrombos Diathes haemorrh (Stuttg.). In press.
Chella, U. & Lorenchi, C. Ann Ostet Ginec 76 207 1954
Edson, J R., Blaese, R. M., White, J G. & Krivit, W *J Pediat* 72 342, 1968.
Forgács, J Zbl Gynäk 85 695 1962.
Nielsen, N C. Acta obstet gynec scand *48* 371 1969
— Acta obstet gynec scand 48. 392, 1969 *b*
— Acta obstet gynec scand 48 505 1969 *d*
— Acta obstet gynec scand *37* 195 1958.
— Acta obstet gynec scand *42* Suppl. *2* 1963.
Skjødt, P Acta obstet gynec scand 46. 41 1967
Stark, C. R., Abrahamson, D & Erkan, V Lancet *1* 1180, 1968.
Valentine, G. H. *12* 462, 1958.

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MONOAMNIOTIC TWINS

A Case with Vessel Anomaly in one Twin's Umbilical Cord

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Abstract. A case of monoamniotic twins is reported where both children survived without demonstrable malformations. One twin had aplasia of one umbilical artery. Upon study of the literature this anomaly in liveborn, healthy monoamniotic twins is found to have been described only once before.

Monoamniotic twins are identical twins who are found in the same sac of the membranes, i.e. they share the amnion as well as the chorion.

This type of twin pregnancy is rare; the frequency is recorded as from 2–3% of all twin pregnancies (Trolle, 1958, Simonsen, 1966, Wharton et al. 1968) to 1.2‰ in older papers. In the American literature where this type of twin pregnancy is especially mentioned, approximately 100 cases have been reported, and reviews of these were made by Quigley in 1935, Wensinger & Daly in 196., and Timmons & Alvarez in 1963. In the Scandinavian literature 10 cases have been reported, a review of these was made by Simonsen in 1966.

Monoamniotic twin pregnancy carries an increased rate of perinatal mortality as both fetuses survive in only 40–50% of the cases (Benirschke & Driscoll, 1967, Simonsen, 1966, Timmons & Alvarez, 1963). Fifteen per cent of the babies had congenital malformations (de Leeuw 1965), most often within the central nervous system and the cardiovascular system.

It is thought to be of interest to report another case of monoamniotic twins where both babies survived and one had aplasia of one umbilical artery.

CASE HISTORY

The patient was a 23-year-old primigravida whose sisters are dizygotic twins. Since the age of 14 she had menstruated regularly. The last menstruation started on April 3, 1967 and the date of confinement was estimated to be around January 10, 1968. During the 29th week of pregnancy the patient was referred to the outpatients clinic of the ward owing to a suspicion of twins, and by means of fetal electrocardiography the diagnosis was confirmed. During the 33rd–34th weeks of pregnancy the patient was hospitalized in order to get adequate rest. Everything seemed to be normal except for a rather excessive increase in weight. Two weeks before the expected date of confinement she was again hospitalized because of slight uterine contractions. Her weight during the pregnancy period had then increased by 22 kg. On examination of the patient abundant amniotic fluid and slight crural oedema were found; the blood pressure was normal and there was no albuminuria. The patient's blood type was B Rhesus positive. Forty-eight hours after hospitalization clear amniotic fluid started to ooze out, after that the labour pains commenced, and after 9 hours the patient felt second stage labour pains. On vaginal exploration a head was found in a deep anterior vertex presentation. A pudendal block was made with 20 ml Xylocain 1% with noradrenalin, and as the cardiac frequency immediately after this became slow (6–8/5 sec), episiotomy was performed and Kielland's forceps was applied. Twin A was easily extracted. At once twin B's umbilical cord prolapsed from the vulva. The two umbilical cords were intertwined in several windings, but there were no knots. After twin A's delivery there was no further loss of amniotic fluid. It was then obvious that it was a case of monoamniotic twins. Upon further exploration a head was felt at the level of the ischial spines in an irregular vertex presentation; no membrane was felt. The heart frequency was slow 5–8/5 sec. After syntocinon 0.3 ml i.m. twin B was delivered by vacuum extraction 9 min after twin A. The placenta separated a few minutes later and was expelled by light pressure in the uterine fundus.

The placenta weighed 600 g and measured 20 by 22 cm. Two umbilical cords were found to be inserted in the central part of the placenta, spaced 3 cm apart. There was no septum between them (Fig. 1). Twin A's umbilical cord measured 70 cm, twin B's 60 cm. Twin A's umbilical cord contained only one umbilical artery

month of pregnancy and at birth. This procedure would, no doubt, lower the perinatal mortality of monoamniotic twins but, on the other hand, it does not seem reasonable to subject the 97% of women who bear diamniotic twins to an examination which is not totally without danger.

According to Corner's (1955) theory monoamniotic twins will develop when the inner cell mass of the egg divides between the 7th and the 13th day after conception, i.e. at a time when the amniotic cavity is formed. If the division takes place still later it becomes incomplete and the fetuses will be conjoined (so-called Siamese twins). The late division is possibly correlated with the *increased rate of congenital malformations* in monoamniotic twins. Going through the literature from 1935 to 1965 de Leeuw (1965) found malformations in 15% of the cases. It involved 15 children, in 13 cases there was a malformation in one and in 1 case in both twins. Meningocele, anencephaly and congenital heart disease were found most often. It is characteristic that as a rule only one twin is malformed, which excludes a common genetic cause.

In the case reported here the only anomaly found was aplasia of one umbilical artery in the first twin. In spite of this the twins had the same weight at birth and the same haemoglobin concentration, which indicates that there has been haemodynamic equilibrium between the two fetuses circulation. Aplasia of the umbilical artery is found in ½–1 of all new-born infants. *Benirschke & Driscoll* (1967) indicate that the frequency is higher in twins. After examining 250 consecutive twin pregnancies they found the anomaly in 18 out of 500 fetuses (3.6%). However other authors have not been able to confirm this. Papadatos & Paschos (1965) found, after examining 108 twins, no cases of aplasia of the umbilical artery and among 106 twin pregnancies *Kristoffersen* (1969) found only one child with aplasia of the umbilical artery. On the other hand, it seems to have been established that aplasia of the umbilical artery is accompanied by a perinatal mortality rate of 15–20% and malformations appear in 25–50% (Benirschke & Driscoll, 1967 Kristoffersen, 1969; Papadatos & Paschos, 1965).

A search of the literature reveals that aplasia of the umbilical artery in one of monoamniotic twins has only been described 3 times earlier. Hyrtl (1870) found the anomaly in one of monoamniotic twins, it was a case of a twin birth during the 7th month, and the looks and fates of the fetuses were not described. Besides Wharton et al. (1968) have described aplasia of the umbilical artery in one monoamniotic twin. They found the anomaly in 2 cases among 18 monoamniotic pregnancies. In one case it was an acardiac monster where aplasia of the umbilical artery is the rule. In the second case the anomaly was found in a liveborn child without malformations.

Thus the case reported here is probably the second known case with aplasia of the umbilical artery *in one of a pair of monoamniotic twins* and in spite of this, survival of both children without demonstrable malformations.

Addendum. Recently there has been another case of monoamniotic twins in our obstetrical department. The patient was a 32-year-old primigravida who in the 32nd week of pregnancy went into labour and after 10 hours, delivery of two girls with birth weight 1500 g and 1700 g was accomplished spontaneously in 3 min. There were no cord complications at the birth. The placenta was monoamniotic but otherwise normal. Both cords contained three vessels. The children had respiratory failure from birth and died a few hours later. Autopsy revealed in both primary atelectasis of the lungs, no congenital malformations were found.

REFERENCES

Benirschke, K. & Driscoll, S. G. The Pathology of the Human Placenta. Springer Verlag, Berlin, Heidelberg and New York, 1967.

Corner, G. W. Amer J Obstet Gynec 70 933, 1955.

Dunnihoo, D. R. & Harris, R. E. Amer J Obst Gynec 96 894, 1966.

Hyrtl, J. Die Blutgefässe der Menschlichen Nachgeburt in normalen und abnormen Verhältnissen. W. Braumüller, Vienna, Austria, 1870.

Kristoffersen, K. Acta obstet gynec scand 48 195, 1969.

de Leeuw, J. H. A. Ned T Verlosk 64 295, 1965.

Papadatos, C. & Paschos, A. Obst & Gynec 26 367, 1965.

Quigley, J. K. Amer J Obstet Gynec 29 354, 1935.

Salomonsen, M. Acta obstet gynec scand 45 43, 1966.

Timmons, J. D. & de Alvarez, R. R. Amer J Obstet Gynec 86 875, 1963.

Trolle, D. Nord Med 59 191, 1958.

Wensinger, J. A. & Daly, R. F. Amer J Obstet Gynec 83 1254, 1962.

Wharton, B. Edwards, J. H. & Cameron, A. H. J Obstet Gynaec Brit C Wth 75 158, 1968.

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Fig 1 The central part of the placenta. Twin A's umbilical cord to the left. No septum. Numerous vessel anastomoses.

which was established upon an examination of cross section near the umbilicus. A histological examination revealed a normally structured placenta and two umbilical cords with . and 3 essels respectively (Figs. 2 and 3)

The twins were boys and both weighed 2400 g at birth. They cried spontaneously at once. They had no external malformations. Later electrocardiograms and X-ray aminations of the lungs and the heart were made these examinations showed normal conditions. The boys blood type was A, Rhesus positive and their haemoglobin concentration was 19.5 and 19.6 g per 100 ml, respectively They thrived on breast-feeding and were discharged, to-

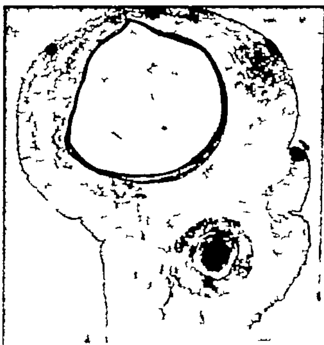


Fig Microphotograph. A cross section of twin A umbilical cord containing only 2 essels; 1 artery and 1 ein. The ein is dilated and degenerati changes are found in the ascular wall.

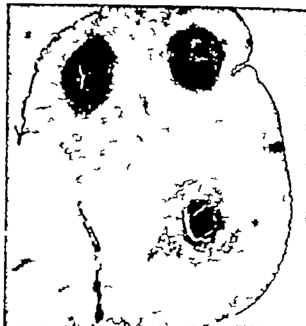


Fig 3 Microphotograph. A cross section of twin B's umbilical cord containing 3 vessels; arteries and 1 ein.

gether with their mother 1 days after birth. At an examination 10 weeks after birth they both eighed 4700 g and showed nothing abnormal.

DISCUSSION

The high perinatal mortality rate in connection with monoamniotic twins is first and foremost due to complications originating from the umbilical cords, especially knots, which may lead to intrauterine death of one or both fetuses. Often there will be a prolapse of the second twin's umbilical cord after the first twin's birth, and all authors therefore agree that the second of monoamniotic twins ought to be delivered as quickly as possible in order to improve its chances. As in the case reported the diagnosis may be made after the first twin's birth, partly on the basis of the two intertwined umbilical cords, possibly with knots, partly on the basis of a vaginal examination where the presenting part of the second twin will be found directly there will be no amniotic sac.

Dunnihoo & Harris (1966) diagnosed monoamniotic twins before birth by amniography and consider the possibility of doing routine amniography in the 36th week on all women with twinpregnancies in order to find the few cases of monoamniotic twins. They also recommend delivery by Caesarean section in the 36th week in order to avoid cord complications during the last

month of pregnancy and at birth. This procedure would, no doubt, lower the perinatal mortality of monoamniotic twins but, on the other hand, it does not seem reasonable to subject the 97% of women who bear diamniotic twins to an examination which is not totally without danger.

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REFERENCES

Benirschke, K. & Driscoll, S. G. The Pathology of the Human Placenta. Springer Verlag, Berlin, Heidelberg and New York, 1967
Corner G. W. Amer J Obstet Gynec 70 933, 1955
Dunnihoo, D. R. & Harris, R. E. Amer J Obst Gynec 95 694, 1966.
Hyrtl, J. Die Blutgefässe der Menschlichen Nachgeburt in normalen und abnormen Verhältnissen. W. Braumüller Vienna, Austria, 1870
Kristoffersen, K. Acta obstet gynec scand 48. 195 1969
de Leeuw J. H. A. Ned T Verlosk 64 295 1965
Papadatos, C. & Paschos, A. Obst & Gynec 26 367 1965.
Quigley J. K. Amer J Obstet Gynec 29 354, 1935
Simonsen, M. Acta obstet gynec scand 45 43, 1966.
Thomson, J. D. & de Alvarez, R. R. Amer J Obstet Gynec 86, 875, 1963
Trolle, D. Nord Med 59 191, 1958.
Wensinger J. A. & Daly R. F. Amer J Obstet Gynec 83 1254, 1962.
Wharton, B. Edwards, J. H. & Cameron, A. H. J Obstet Gynaec Brit C'lth 75 158 1968.

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THE PROGNOSIS OF THREATENED ABORTION

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Abstract Of 266 patients admitted with threatened abortion, 135 (50.8%) aborted, while 131 (49.2%) gave birth to 106 full term children and 25 premature children. Three of these children suffered from malformations. The risk of abortion was greater the earlier in pregnancy the symptoms occurred, and the longer and more severe the haemorrhage. In addition the frequency of abortion increased with increasing maternal age, with an increasing number of pregnancies, and if the patient had had previous legal abortion, whereas earlier spontaneous abortion did not affect the prognosis. The frequency of abortion also rose in the lower social groups, and was particularly high among the unmarried women. The risk of a premature child was 3 times greater after threatened abortion than after a normal pregnancy. The perinatal mortality was not increased in full term children, but among the premature children it was found to be very high, in fact many times higher than among premature children as a whole.

A frequent cause of haemorrhage during the first months of pregnancy is threatened abortion (T.A.); according to Hertig (1944) the condition occurs in at least 16 per cent of all pregnancies.

A number of investigators have attempted to evaluate the prognosis for T.A. but the results, owing to different definitions of the term T.A., are very different and not comparable.

Thus Kaye (1953) found that virgin haemorrhage of short duration did not affect the remainder of the pregnancy. On the other hand Hansen (1963) and Holtstein (1958) both found that approximately 50 per cent of all T.A. ended in abortion, while Alkner (1969) and Turnbull (1956) found a frequency of abortion of approximately 20 per cent.

There are similarly very different opinions regarding the development of the foetus in the present series. Thus Kaye (1953) states that the risk of malformation is not increased after T.A. The majority of investigators, however, consider that malformation is slightly more frequent following T.A. than after an uncomplicated pregnancy (Burger, 1951 Holtstein 1958), and finally a single investigator (Asantl, 1963) states that the risk of malformation is 12%.

A number of articles on T.A. have appeared in the Scandinavian literature (Alkner 1960 Asantl, 1963 Fuchs, 1963 Hansen, 1963 Høglund, 1961 Møller 1966 Lundsteen, 1941 Pedersen, 1966), but the great majority are concerned with the question of whether hormone treatment improves the prognosis of T.A. and only in a very few studies has the prognosis been studied in relation to certain clinical and anamnestic factors (Alkner 1960; Asantl, 1963 Hansen, 1963).

The object of the following study has been to evaluate the prognosis of T.A. and in addition the influence of different anamnestic and clinical factors on the prognosis have been examined.

MATERIAL

In this study the term T.A. is defined as haemorrhage from the uterus in association with an intrauterine pregnancy prior to 20 weeks gestation, with the cervix incompletely effaced and the os closed, and irrespective of whether or not uterine contractions are occurring. (Ugeskr. læger 1964; Nomenclatura obstetricia, 1959.)

A total of 271 patients were admitted to Maria Hospital, Vejle, with T.A. in the period 1.1.1950–31.12.1966. Of these it was possible to trace 266 for follow-up examination, the other 5 patients, who could not be traced, are not included in the material.

In all cases the diagnosis was confirmed at gynaecological examination carried out immediately after admission.

During hospitalization 201 patients were treated conservatively (rest in bed and sedation), while 65 patients were treated with progesterone. The frequency of abortion was, however, the same in both groups (approximately 50%), and as a critical survey of the literature

Table I *Number of births and the perinatal mortality in various weight groups*

Weight	1 000– 1,500 g	1,500– 2,000 g	2,000– 2,500 g	*Total* under 2,500 g	Over 2,500 g
No born	9	4	12	25	106
Mortality %	100	50	25	36	0.9

(Fuchs, 1963) has shown that progesterone treatment does not improve the prognosis of T.A., the material has been treated as a whole.

RESULTS

135 (50.8%) of the patients miscarried, 43.7% of the abortions occurred within the first week of admission, while 80% occurred within one month of admission.

The remainder of the patients—131 (49.2%) gave birth to 106 full term and 25 premature children, the weight of the children and the perinatal mortality in the various weight groups are shown in Table I.

Three children suffered from malformations—in two cases this consisted of morbus cordis and in one case of spina bifida and myelocele

The majority of patients, as is shown in Table II were admitted in the 9th–12th week of pregnancy The table also shows that the later in pregnancy the patient was admitted the less was the risk of abortion, while the risk of having a premature child and the perinatal mortality was greater

Both the amount and duration of the haemorrhage influenced the prognosis of T.A., so that the risk of abortion became greater both with severe haemorrhage and with haemorrhage of long duration (The term severe haemorrhage is used in this connection to define a haemorrhage that is more severe than that occurring during menstruation or where blood clots were passed) The severity of the symptoms was also related to the incidence of premature births and with the perinatal mortality (Table III)

The great majority of the patients were in the age group 20–29 years. The age groups 20–24 and 25–29 years contained equal numbers. The frequency of abortion, of premature children and of perinatal mortality was lowest for the age group 25–29 years in both younger and older women all these factors were increasingly more frequent (Table IV)

The majority of patients in the series were primigravidae. The frequency of abortion and of premature children was lowest for the secundi-

Table II *The course of the pregnancy in relation to the time of admission*

Admitted in week of pregnancy	No. of pat.	Abortion (%)	Births (%)	Total born	Premature (%)	Perinatal mortality %
– 8	20	70	30	6	33.3	33.3
9–12	127	53.5	46.5	59	13.6	5.1
13–16	74	43.2	56.8	42	21.4	14.3
17–20	45	46.7	53.3	24	25	16.7
Total	266	50.8	49.2	131	19.1	11.4

Table III *The course of the pregnancy in relation to the severity and duration of the haemorrhage*

Severity of symptoms	N of pat.	Abortion (%)	Births (%)	Total born	Premature (%)	Perinatal mortality
Slight haemorrhage less than 1 day	34	2.9	97.1	33	9.1	9.1
Severe haemorrhage less than 1 day	26	7.7	92.3	24	16.7	4.2
Slight haemorrhage less than 7 days	60	33.3	66.7	40	15	2.5
Slight haemorrhage more than 7 days	52	63.5	36.5	19	36.8	21.1
Severe haemorrhage single 1 day Slight haemorrhage less than 7 days	65	81.5	18.5	1	25	25
Severe haemorrhage single 1 day Slight haemorrhage more than 7 days	26	92.3	7.7	2	50	100
Severe haemorrhage several days	3	66.7	33.3	1	100	100

Table IV *The course of the pregnancy in relation to the age of the patients*

Age in years	No. of pat.	Abortion ( )	Births (%)	Total born	Premature (%)	Perinatal mortality
20	21	62 9	37 1	8	0	0
20–24	81	50 6	49 4	40	27 5	20
25–29	83	39 8	60 2	50	8 0	4 0
30–34	47	61 7	38 3	18	27 8	11 1
35–39	28	53 6	46 5	13	30 8	15 4
40–44	6	66.7	33 3	2	50 0	50 0

gravidae and thereafter increased with gravidity I contrast, there was no definite relation between the perinatal mortality and the number of pregnancies (Table V).

Previous spontaneous abortions did not change the prognosis f T.A whereas the frequency of abortion was considerably increased amongst patients that had previously had a legal abortion ho the children that were born of these patients were premature and the perinatal mortality very high (Table VI).

Finally an attempt has been made to evaluate the prognosis of T.A. in relation to the social status of the patient. The division of the patients into social groups has been carried out according to the grouping used by Svalastoga (1959) The author is aware of the fact that some uncertainty occurs in grouping the patients according to informations contained in the case history but it is considered that the relationship between the different groups is almost correct.

The grouping is based on the following scheme:

Group 4 Owners of businesses employing between 25–100 employees. Employees or civil servants ith university or similar education.

Group 5 Owners of businesses with 5–25 employees. Employees in charges of 10–50 persons, or who have position requiring an education corresponding to the University Entrance examination.

Group 6 Owners of businesses with 1–5 employees. Employees with 9–10 years education or ho are in charge of 1–10 other employees.

Group 7 Owners of one man businesses ho only have family help. Tradesmen ith an apprenticeship, or similar special training.

Group 8 Labourers. The less affluent of the self employers.

Table V *The course of the pregnancy in relation to the number of completed pregnancies (including the present)*

Pregnancy	No of pat	Abortion ( )	Births ( )	Total born	Premature (%)	Perinatal mortality
1	81	54 3	45 7	37	16 2	8.1
2	68	45 6	54 4	37	13.5	10 8
	59	50 8	49 2	29	24 1	6 9
	31	51 6	48 4	15	26 7	26.7
5	12	66 7	33 3	4	25 0	25 0
More than 5	15	40	60	9	22.2	11 1

Table VI *The course f the pregnancy in relation to previous abortions*

Abortions Type	No	No of pat	Abortion (%)	Births (%)	Total born	Premature ( )	Perinatal mortality
	0	185	50 3	49 7	92	16 3	9 8
	1	54*	51 9	48 1	26	23.1	19.2
Spontaneous	2	18	50 0	50 0	9	11 1	0
More than		3	33 3	66 7	2	50 0	0
Legally induced	1	7*	71 4	28 6	2	100 0	50 0

One patient ith both spontaneous and legally induced abortion

Table VII *The course of the pregnancy in relation to the social status of the patient*

Social group	No of pat.	Abortion (%)	Births ([illegible])	Total born	Premature (%)	Perinatal mortality
4	8	12.5	87.5	7	14.3	0
5	15	40.0	60.0	9	33.3	33.3
6	69	43.5	56 5	39	[illegible]	7 7
7	111	58 6	41 4	46	19.6	6.5
8	63	52.4	47 6	30	23.3	20.0
Unmarried	18	72.2	27 8	5	20.0	0
Married	248	49.[illegible]	50.8	126	19.0	11.9
+ employment	72	56.9	43 1	31	19 4	6.5
÷ employment	194	48.5	51.5	100	19 0	13 0

It was found that the abortion rate and frequency of prematurity increased in the lower groups whereas the perinatal mortality appeared to be independent of the social status of the patient

The frequency of abortion was considerably above average among the unmarried women. On the other hand the frequency of abortion among employed patients was only slightly higher than among patients that were unemployed. The frequency of prematurity was the same in both groups while the perinatal mortality was highest among the unemployed patients (Table VII).

DISCUSSION

If one attempts to compare different series of T.A. one finds that this is often impossible due to the different definitions of T.A. in the studies. Thus Asanti (1963) and several others speak of T.A. also in cases where uterine contractions occur without haemorrhage. These cases are not included in the present series, inasmuch as it was considered that a diagnosis of T.A. based on this often subjective symptom would be uncertain. In contrast to this it can be mentioned that Alkner (1960) in his study excluded all the cases where abortion occurred within 1 week of the cessation of haemorrhage as he considers these cases as spontaneous abortions. Alkner thus found a frequency of abortion of 19.4 following T.A. These cases are included in the present series, inasmuch as the patients at the time of admission suffered from T.A. according to the definition. Finally many investigators have not stated which definition was used in the selection of their material. It is thus clear that a direct comparison between the different studies with regard to the prognosis of T.A. is not possible, and that the results will be very different.

In series that can be compared with that presented here (Hansen, 1963 Holstein 1958) there is agreement in the frequency of abortion, viz. approximately 50%. A large percentage of the abortions occurred shortly after admission Hansen (1963) found, by histological examination of his material, that in those cases in which abortion occurred shortly after admission there were such distinct regressive changes (fibrosis, necrosis) in the placenta that the ovum could not possible have been alive at the time of admission.

The risk of abortion was greater the earlier in the pregnancy the haemorrhage took place The same was found by Alkner (1960) this must be seen in the light of the fact that an abortion in the early stages of a pregnancy often results from a defect in the ovum (Hertig & Rock, 1949) In these cases the haemorrhage begins on average in the 8th week of pregnancy and the abortion occurs on average 13 days later (Colvin, 1950). Similarly prolonged and severe haemorrhage more frequently resulted in abortion than brief and slight haemorrhage, a finding confirmed by Alkner (1960) The explanation of this can be that the uteroplacental seperation becomes more pronounced after prolonged and severe haemorrhage so that the foetus has poor conditions in which to survive (Javert, 1957).

With regard to the age of the mother and the number of pregnancies there was also correlation between Alkner's and the present series, inasmuch as both show that the frequency of abortion increased with age and with an increasing number

of pregnancies. This must be seen in relation to the fact that the number of abnormal foetuses increases with age (Mahon, 1954).

Previous spontaneous abortion does not change the prognosis of T.A. On the other hand was the frequency of abortion considerably increased among patients that had a previous legal abortion. The cause of this could be the previous operative procedure, but is more likely due to the fact that a woman who has previously had a legal abortion is often not particularly interested in carrying through a new pregnancy. Thus are these patients more often admitted for spontaneous abortion than for T.A. (Johannsen, 1970).

The frequency of abortion increased in the lower social groups. One dare not express an opinion as to the reason of this but these patients, as is in the case with patients with previous legal abortions, are relatively rarely admitted for T.A. (Johannsen). A considerable number of unmarried women aborted this can be caused by the fact that the desire to carry through the pregnancy has not been particularly strong, and therefore they have stopped treatment.

The frequency of prematurity in the series was 19.1 which is in greement with that found by other investigators; thus Tosetti (1960) found 19.3% Asanti (1963) 20.7% and Turnbull (1956) 20.9% while Alkner (1960) only found 12.7% premature children in his material. No definite figure is available for the frequency of prematurity in a normal series in this department, but other investigators state that this normally lies between 5–9% (Alkner 1960; Turnbull, 1956; Tosetti, 1960). In other words the risk of a premature birth is approximately 3 times as great after T.A. than after normal pregnancy.

The perinatal mortality (P.M.) for the whole series was 11.4. Tosetti (1960) found a P.M. of 11.8% in his material. This is largely due to the very high P.M. among premature children. In this series P.M. was for the full term children 0.9% which is not higher than normal. On the other hand the P.M. for the premature children was 56%. Alkner (1960) found P.M. among premature children after T.A. of 47.8%. Turnbull (1956) found 47.5%. The P.M. among premature children after an uncomplicated pregnancy is stated by Turnbull to be 27.9% and by Alkner to be 19.3%. the P.M. for premature children is increased several times after T.A. possibly because a large number of the premature children have a very low birth weight.

There is considerable disagreement between the different studies with regard to the frequency of malformations. The majority consider that the frequency is slightly increased after T.A. Thus Turnbull (1956) found 3.6% Alkner (1960) 4.4% and Burges (1951) 1.5% malformations. Asanti (1963) found 4.6% malformations in an obstetrical department, but in a follow-up study of a small part of the series showed the figure of 11.4%. However Hollstein (1958) concluded in his study that as the risk of malformation is very slight every possible attempt should be made to maintain pregnancy.

REFERENCES

Alkner N et al. Nord Med 63 261 1960.

Asanti, R. et al. Acta Obstet Gynec Scand 42 107 1963.

Burges, E. S. Am J Obst Gynec 61 615, 1951.

Colvin, E. D et al. Am J Obst Gynec 59 1208 1950.

Fuchs, F. Ugeskr læger 125 1283, 1963.

Hansen, H. et al. Acta Obstet Gynec Scand 42 117 1963.

Hertig, A. T et al. New England J Med 230 797 1944.

Hertig, A. T & Rock, J. Am J Obst Gynec 58 968, 1949.

Hollstein, K. Zentralbl Gynäk 80 16, 1958.

Hølund, T. Nord Med 41 1401, 1961.

Javert, C. T. Spontaneous and habitual abortion. Mc Graw-Hill, New York, 1957.

Johannsen, A. Acta obstet gynec scand 49 93 1970.

Kaye, R. M. et al. Am J Obst Gynec 65 109 1953.

Lundberg, A. Nord Med 12 2999 1941.

MacMahon, B. et al. Obst Gynec 4 477 1954.

Møller K. J. A. et al. Ugeskr læger 128 1457 1966.

Pedersen, E. et al. Ugeskr læger 128 1362, 1966.

Svalastoga, K. Prestige, Class and Mobility. Gyldendal, Scandinavian University Books, 1959.

Tosetti, K. Geburtsh. Frauenh 20 513, 1960.

Trolle, D. Nomenclatura obstetricia, CIBA, 1959.

Turnbull, E. et al. J Obst & Gynec Brit Emp 63 553 1956.

Ugeskr. læger Lederartikel, 128 1480, 1966.

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THREATENED AND SPONTANEOUS ABORTION

A Retrospective Study of the Diagnosis on Admission

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Abstract A survey has been made of the case histories of 271 patients admitted to hospital because of threatened abortion and 436 patients admitted because of spontaneous abortion. The object of the study was to find some factor in the history that could explain why a number of patients are admitted to hospital at a time when abortion threatens and others at a time when the abortion is in process, as judged by the initial diagnosis.

It was found that patients with threatened abortion are hospitalized earlier in pregnancy than patients with spontaneous abortion. In addition it was seen that admission because of threatened abortion was most frequent among younger patients (below 30 years of age), among primigravidae and among patients from the upper social groups. While admission because of spontaneous abortion was most frequent among the older patients (above 35 years of age), multigravidae, unmarried women, patients that had a previous legal abortion and, finally among patients from the lowest social groups. Possible reasons for these findings are discussed.

It is concluded that a number of abortions could possibly be avoided if patients with symptoms of abortion were admitted to hospital for effective treatment as early as possible after the symptoms become manifest.

A common complication in the early months of pregnancy is haemorrhage. Amongst hospital admissions this occurs most frequently in connection with spontaneous abortion (S.A.) and secondly in connection with threatened abortion (T.A.) (Javert, 1943).

A number of patients admitted for T.A. will later have an abortion, while others will be able to continue the pregnancy (Alfkner 1960, Asmil, 1963, Hansen, 1963). In some cases the symptoms will subside when the patient is put to bed, but the condition will often recur when she is mobilised.

Nilsson (1957) and Hertig (1949) have both found that there is no theoretical basis for successful prophylactic treatment of the abortion in two thirds of all spontaneous abortions. While Nilsson does not draw any conclusions regarding the remaining third, Hertig concludes that there is a theoretical possibility of avoiding one third of all spontaneous abortions at the time the patient is first seen by her doctor.

Nilsson also found that in 15% of the patients admitted because of spontaneous abortion, the duration of the symptoms before abortion occured was less than 24 hours. In such cases it is not to be expected that the patient will be admitted to hospital while the abortion is only threatened, but providing the symptoms are of longer duration there is the possibility of admission.

Thus Colvin (1950) found that in cases where the abortion resulted from a blighted ovum—the most frequent cause of abortion—the symptoms on average began in the 8th week of pregnancy while the abortion occurred 13 days later i.e. that the symptoms were of such long duration that these patients could have been admitted to hospital at a time when the abortion only threatened.

The object of the present study has been to survey the material in order to discover whether there were factors in the case histories that could explain why a number of patients are admitted to hospital for abortion at a time at which the abortion only threatens and why others are first admitted at a later period when the abortion is already in progress.

MATERIAL

In this study the term T.A. is defined as haemorrhage from the uterus in association with an intrauterine preg-

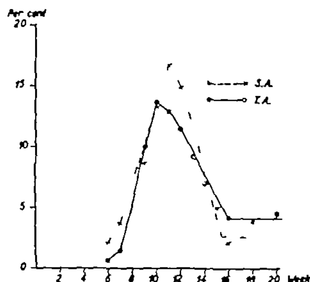


Fig 1 The duration of the pregnancy at the time of admission.

nancy prior to 20 weeks gestation, with the cervix incompletely effaced and the os closed, and irrespective of whether or not uterine contractions are occurring. (U.I.L., 1966, Nomenclatura Obstetricia, 1959).

The term S.A. is used to denote haemorrhage from the uterus in association with an intrauterine pregnancy prior to 20 weeks gestation, with the os open, and possibly with the passing of fragments of ovum or a whole ovum *immediately* prior to dmission, in other words S.A. includes the unavoidable, the incomplete and the complete abortion.

S:t Maria Hospital, Vejle, receives patients from a mixed urban and rural district. 71 patients wer d-mitted with T.A. in the period 1 1 1950 to 31 12.1966. In the same period 1721 patients were admitted with S.A., *of these all the patients admitted to the department in* the period 1 1 1957 t 31 1..1961 were included in the study a total of 436 patients (25.3%).

RESULTS

The time of admission in relation to the first day of the last menstruation

The majority of admissions because of S.A. occurred in the 11th week of pregnancy while the majority of admissions because of T.A. occurred in the 10th week. The admissions for both T.A and S.A. showed an evenly falling tendency prior to and after these periods. Admission because of S.A. was relatively more frequent than because of T.A. in the first 3 months of pregnancy while admission because of T.A. was relatively more frequent after this time (Fig. 1 Table I).

Table I. *Duration of pregnancy at time of admission*

Week	T.A. %	S.A., %
– 8	7 4	16.4
9–12	48.0	51 6
13–16	27 7	19 7
17 20	17 1	10.1

Table II *The age of the patient at the time of admission*

Age years	T.A., %	S.A., %
–19	8.1	6.8
20– 4	30.3	26.4
25–29	31.0	25.5
30–34	17 7	16.7
35–39	10 7	15.1
40–44	2..	8.7
45–	0	0 7

Age and number of pregnancies

Prior to the age of 30 years relatively more patients were admitted with T.A. than with S.A after the age of 35 the figures were reversed. In the age group 30 to 35 years there was an equal number in the two groups (Table II).

From Table III it can be seen that relatively more primigravidae were admitted because of T.A than S.A. while admission because of S.A. was relatively more frequent among the multi gravidae.

However as the incidence of abortion increases with both increasing age and with an increasing number of pregnancies (Javert, 1957) an attempt has been made in Fig. 2 to .. these two factors. Thus the distribution between T.A. and S.A. are put in relation to both age and the number of pregnancies.

Previous abortions

Table IV shows the distribution and the type of previous abortions in the series. One patient admitted with T.A. and two patients with S.A. had previously had both a legally induced abortion and a spontaneous abortion.

Social status

The grouping used by Svalastoga (1959) has been utilized for the division of the material into social groups.

Table III. *The number of pregnancies (including the present)*

Pregnancy	T.A., %	S.A., %
1	30 3	24.1
2	25 5	26 1
3	22 1	21.3
4	11.4	13 3
5	4 8	5.3
Above 5	5.9	9 9

The grouping is based on the following scheme:

Group 4. Owners of businesses employing between 25 to 100 employees. Employees or civil servants with university or similar education.

Group 5. Owners of businesses with between 5 to 25 employees. Employees in charge of 10 to 50 subordinates or who have position requiring an education corresponding to University Entrance Examination.

Group 6. Owners of businesses with between 1 to 5 employees. Employees with 9 to 10 years education or who are in charge of 1 to 10 subordinates.

Group 7. Owners of one man business or who have

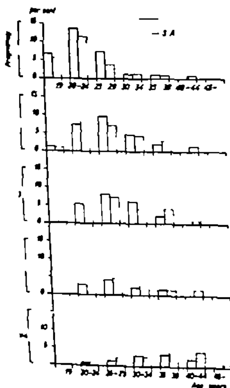


Fig. 2. Admissions in percentage of threatened and spontaneous abortions in relation to age and pregnancies.

Table IV. *Previous abortions and the type*

Abortion	T.A., %	S.A., %
Spontaneous	27.6	25.4
Legally induced	2.6	3 7
Both	29.9	28.7

Table V. *The social status of the patient*

Social group	T.A., %	S.A., %
4	3 0	2.3
5	5 5	3 7
6	25.4	22.9
7	41 7	39 7
8	24.4	31 4
Employed	23 6	26 2
Unmarried	7 4	13 8

only help from the family. Tradesmen with an apprenticeship or similar special training.

Group 8. Labourers. The less affluent of self-employers.

The distribution of the patients in the different groups is shown in Table V. It can be seen that there were relatively more admissions because of T.A. in the upper social groups (4–7) while there were relatively more because of S.A. in the lowest group. In addition it can be seen that there was slight predominance of working women and double as many unmarried women who were admitted because of S.A. than because of T.A.

DISCUSSION

It was not possible to carry out a survey of the duration of the symptoms prior to admission, as the case histories were incomplete in this respect. However it is considered that as patients with T.A. are admitted earlier in the pregnancy than patients with S.A., this can be taken as an expression of, that patients with T.A. are admitted earlier after the occurrence of the symptoms than those with S.A.

The majority of admissions because of both T.A. and S.A. occurred in the 8th to 12th week of pregnancy with a maximum for T.A. in the 10th week and for S.A. in the 11th week. This is in agreement with the study of Javert (1957) with regard to S.A. It has not been possible to find similar studies of T.A. The reason why most

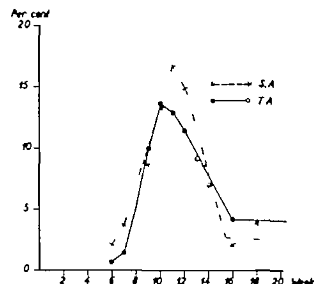


Fig 1 The duration of the pregnancy at the time of admission.

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30–34	17 7	16.7
35–39	10.7	15 1
40–44	2.2	8 7
45–	0	0.7

in the 10th week. The admissions for both T.A and S.A. showed an evenly falling tendency prior to and after these periods. Admission because of S.A. was relatively more frequent than because of T.A. in the first 3 months of pregnancy while admission because of T.A. was relatively more frequent after this time (Fig. 1 Table I).

Age and number of pregnancies

Prior to the age of 30 years relatively more patients were admitted with T.A. than with S.A. after the age of 35 the figures were reversed. In the age group 30 to 35 years there was an equal number in the two groups (Table II).

From Table III it can be seen that relatively more primigravidae were admitted because of T.A than S.A. while admission because of S.A. was relatively more frequent among the multigravidae.

However as the incidence of abortion increases with both increasing age and with an increasing number of pregnancies (Javert, 1957) an attempt has been made in Fig. 2 to combine these two factors. Thus the distribution between T.A. and S.A. are put in relation to both age and the number of pregnancies.

Previous abortions

Table IV shows the distribution and the type of previous abortions in the series. One patient admitted with T.A. and two patients with S.A. had previously had both a legally induced abortion and a spontaneous abortion.

Social status

The grouping used by Svalastoga (1959) has been utilized for the division of the material into social groups.

to information contained in the case histories, but it is considered that the relationship between the different groups is almost correct.

In the upper social groups the admission because of T.A. were slightly more frequent than because of S.A. In these groups there were relatively few working women and at the same time these women generally had fewer children. This in association with the better economic status possibly results in the desire to carry through the pregnancy being greater in this group than in the lower social group where it was found that relatively more were admitted because of S.A. The explanation of this can be that this group included nearly all the unmarried women and a larger number of working women. Finally an extra child would be an extra financial strain. These factors would probably result in such women having less desire to continue with the pregnancy so that the patients are admitted rather late after the occurrence of the symptoms.

CONCLUSION

Patients with T.A. are admitted on an average earlier in pregnancy than patients with S.A. and as a result of this probably also earlier after the occurrence of the symptoms. Admission because of T.A. is relatively more frequent among patients under 30 years of age, among primigravidae and among patients from the upper social groups, while admission because of S.A. is relatively more frequent among older patients, multigravidae, unmarried women, patients that had previously had a legal abortion, and patients from the lower social group. In number of cases such patients are possibly admitted late after the occurrence of the symptoms due to factors connected with the home and in other cases due to the fact that there is no great desire to continue with the pregnancy.

Possibly some abortions could be avoided provided patients with symptoms of abortion were admitted to hospital early after the occurrence of the symptoms, so that they could receive effective treatment such as rest in bed—a form of treatment which is difficult to carry out effectively in the home.

REFERENCES

Aftner, N. et al. Nord Med 63 261, 1960.
Asmal, R. et al. Acta Obstet Gynec Scand 42 107 1963.
Colvin, E. D. et al. Am J Obstet Gynec 59 1208, 1950.
Hansen, R. et al. Acta Obstet Gynec Scand 42 117 1963.
Hertig, A. T. et al. New England J Med 230 797 1944
— Am J Obst Gynec 58 968, 1949
Javert, C. T. Spontaneous and Habitual Abortion, Mc Graw-Hill, 1957
Javert, C. T. et al. Surg Gynec & Obst 76 115 1943.
Kærn, T. Nord Med 44 1277 1950.
Nilsson, L. Acta Obstet Gynec Scand 36 suppl. 7 1957
Trolle, D. Nomenclatura obstetricia, CIBA, 1959
Svalastoga, K. Prestige, Class and Mobility. Gyldendal, Scandinavian University Books.
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of the admissions for abortion occur in this period is probably that the blighted ovum—which is the most frequent cause of abortion—is normally expelled around the 10th week of pregnancy (Colvin, 1950 Hertig & Rock, 1944)

The admissions in the early months of pregnancy because of S.A. were relatively more frequent than admissions because of T.A., this is the result of several factors. Partly a number of illegal abortions are in all probability included in the material and it must be presumed that the majority of these are performed in the first trimester and that most of these patients are admitted to hospital after the symptoms have been present for some considerable time, so when they are admitted abortion is unavoidable. Another factor is that a number of patients early in pregnancy are not aware of the fact that they are pregnant and they think that the haemorrhage is a delayed menstruation. As a result of this they are not admitted before the haemorrhage becomes severe or has continued for some time.

Relatively more admissions occurred because of T.A. than because of S.A. after the 13th week. The reverse arguments are then applicable the patients are now aware of the fact that they are pregnant and in the majority of cases interested in carrying through the pregnancy therefore they are admitted early after the commencement of the symptoms

It is not possible to study abortion in relation to age without taking previous pregnancies into account and similarly a study of abortion in relation to previous pregnancies is not possible without considering the question of age It was found that both T.A and S.A. are related to increasing age and to an increasing number of pregnancies. Therefore in this investigation the combined influence of these two factors on abortion has been studied

The majority of admissions occured with regard to both T.A and S.A. in the age group 20 to 29 years, with an equal number in the two five year periods 20 to 24 and 25 to 29 years. This was also found by Kern (1950) for S.A. whereas Javert (1957) and Nilsson (1957) found that the admissions were most frequent in the 25 to 35 and 25 to 29 age groups respectively

Up until the age of 30 years admissions were more frequent because of T.A. than S.A. Possibly this can be explained by the fact that the majority of patients in this age group have had very few pregnancies. In fact they are often primigravidae, i.e patients who have a great desire to carry through the pregnancy· also an early admission is not impeded by the presence of children requiring attention in the home. On the other hand, after the age of 35 years admission because of S.A was more frequent. The majority of these patients have been pregnant several times, often twice or more Among the patients that already have children the desire to carry through another pregnancy is possibly less and because of children in the home it may be difficult for these patients to be admitted to hospital. They are therefore first admitted to hospital after the haemorrhage has become severe or has been of a long duration. Finally the fact that metrorrhagia becomes more frequent with increasing age may be of importance as a number of patients will possibly consider the menostasis and the subsequent haemorrhage as metrorrhagia, and therefore will first be admitted to hospital late after the commencement of the symptoms.

Previous spontaneous abortions were frequent in both groups. However previous legally induced abortions occurred more frequently among patients admitted for S.A. This can undoubtedly be explained by the fact that patients who have previously had a legal abortion are often not anxious for a further pregnancy

There were double as many unmarried patients admitted with S.A. than with T.A. Possibly because these patients are often not particularly desirous in the pregnancy

More working women were found in the group with S.A. than in the T.A. group. The reason for this can be that all the unmarried women—who as shown, are most frequently admitted with S.A.—were working women, but there is the possibility that a working woman consults her own doctor later than a housewife in order not to loose working time and is therefore admitted later

The social grouping of the patients was, as mentioned, carried out on the basis of Svalastogas grouping. This division into social groups was performed on the basis of 4000 interviews, and regard has been taken in the grouping to the title, education and the number of subordinates.

The author is aware of the fact that some uncertainty occurs in grouping patients according

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SOME OPHTHALMOLOGICAL OBSERVATIONS IN TOXAEMIC AND NORMAL LATE PREGNANCY

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Abstract. Various ocular fundus findings recorded by means of ophthalmoscopy and fluorescein angiography of the fundus towards the end of pregnancy in 11 healthy pregnant women and 13 patients with toxaemia of varying degree were analysed. Ten healthy non-pregnant women formed the control group. The results showed that: (1) The healthy pregnant women showed both normal ocular fundi and changes which must be considered definitely pathological. (2) The toxaemic patients showed both pathological ocular fundus changes and perfectly normal findings. (3) On angiography the healthy non-pregnant women revealed a wide variation in the arterial caliber of the ocular fundus, expressed in terms of the artery/vein (A/V) ratio. (4) Variations of roughly the same degree in the A/V ratio occurred in the healthy and toxaemic pregnant women. (5) The A/V ratio was not correlated with the clinical status.

Ever since von Graefe's (1855) description, angiospastic retinopathy has been a universally known complication in toxaemia. The opinion has often been advanced that the treatment of a toxaemic patient could be planned largely on the basis of the degree of spasm of the arteries of the ocular fundus. This view is shared by e.g. Landesman et al. (1951, 195), Hollwich (1960–1961) and Duke-Elder (1967), whereas Werkö (1948) considers that the ocular fundus appearances in toxaemia do not correspond to the overall clinical picture. This is supported by the finding that pathologic changes in the ocular fundus have even been described in normal pregnancy (Hollwich, 1960; Kyrieleis, 1954), while toxaemic patients may have a normal ocular fundus (Mittelstrass & Wolfhagen, 1948; Landesman et al., 1951; Kyrieleis, 1954).

The vessels of the retina are usually examined by ophthalmoscopy but photography of the ocular fundus, either conventional or combined with fluorescein angiography (Novotny & Alvis, 1961) may be used. All these methods were used in the present study in an attempt to correlate the vascular status of the ocular fundi with the degree of severity of toxaemia.

MATERIAL

The series comprised 10 normal non-pregnant women, 11 normal pregnant women and 13 women with toxaemia of late pregnancy. The toxaemic patients were classified as recommended by the American Committee on Maternal Welfare: 7 patients were allocated to the severe pre-eclampsia group, 2 to the mild pre-eclampsia group, and 4 to the toxaemia group with renal disease prior to the onset of toxaemia. The detailed clinical status of the toxaemic patients is shown in Table 1, where they are listed in descending order of severity.

METHODS

At ophthalmoscopy attention was given to findings associated with angiospasm, such as focal fluctuations in calibre, exudates, etc., but especially to the artery/vein (A/V) ratio. For this purpose, the same part of the ocular fundus was photographed by conventional technique and after angiography using an injection of 2.5 cc 20% fluorescein-sodium solution. Photographs were taken automatically at one-second intervals (Zeiss-Opton "Funduskamera mit Automatik Zusatz"). The same film (Adox KB 17) was used throughout the present study. The conventional and suitable fluorescein angiography photographs were enlarged 30. The arterial and venous diameters were measured with a graded loupe, at a point near the papilla where the artery and vein ran side by side and had equal numbers of branches as counted from the papilla. Points with focal arteriolar spasm were not accepted for measurement.

...ntal weight (g)	Maximum protein excretion (week of pregnancy)	Maximum blood pressure during pregnancy	Method of delivery
390	7 0/32	190/115	Section
450	6 4/26	180/110	Spontaneous
000	8 5/38	165/120	Spontaneous
300	7 8/39	170/110	Section
930	9 8/37	180/120	Section
250	2 7/26	200/120	Spontaneous
	8 1/36	200/140	Section
250	3 3/34	160/110	Section
030	1 6/38	140/90	Spontaneous
900	8 3/37	160/110	Induced
380	4 2/38	180/130	Induced
	1 7 40	155/100	Pregnancy continues
150	3 7 37	150/100	Induced

sidered necessary to present in detail the information obtained by this technique. As seen from Fig. .., the vascular contours in the conventional photograph *are much more obscure than in the* angiographs, so much so that no reliable conclusions can be drawn e g as to the A/V ratio.

Fig. 1 shows the A/V ratio of the whole series measured from fluorescein angiographies. The A/V ratios for the normal non-pregnant women ranged from 0 60 to 0 90 mean 0 73 The figures for the normal pregnant women were 0.63–0.89 mean 0.72, and for the toxaemic patients 0.55–0.94 mean 0 74 No significant differences were demonstrable between the groups.

Fig. 3 shows the correlation between the clinical severity of toxaemia and the A/V ratio of these patients. In the left hand vertical column the increasing A/V ratio is shown (corresponding to decrease in the arterial spasm). On the right, the same cases in descending order of clinical severity The figures refer to patients mentioned in Table I. The criteria for clinical degree of severity were: duration of pregnancy at the onset of toxaemia, duration of hospitalization, daily quantity of proteins excreted, blood pressure level at the time of examination, and the child's birth weight. Although the classification is relati ely approximate, the conclusion that no correlation exists between the degree of severity of toxaemia and the A/V ratio can hardly be avoided. It may be pointed out, in addition, that separate comparisons of A/V ratio with the systolic, diastolic and mean blood pressures revealed no better correlations, although the findings are not presented in tabulated form here.

Finally when the patients were placed in a





Fig. Right, conventional fundus photography N B the diffuse vascular contour Left, the same artery with fluorescein angiography Magnification, 90 (film Adox KB 17).

Table I *Clinical data of the toxaemic patients in decreasing order of severity*

Case no	Age	Parity	Classification of the toxaemia	Opthalmologic examination (week of pregnancy)	Protein excretion at the time of examination	Blood pressure at the time of examination	First signs of toxaemia (week of pregnancy)	Stay in hospital (weeks)	Duration of (eeks)
1	42	III	Severe	32	7.0	185/100	24	6	3
2	36	II	Severe	27	1.5	140/100		10	34
3	21	II	Severe	36	6.4	150/105	32	8	39
4	30	II	Severe	36	0.3	140/90	32	6	39
5	[illegible]	I	Severe	35	4 4	150/110	20	5	37
6	30	II	Subacute nephritis	27	0.5	150/100	24	4	39
7	33	V	Severe	36	0.3	170/120	24	5	37
8	22	I	Severe	34	1 0	150/110	34	5	37
9	20	I	Mild	38	1.6	140/80	35	3	39
10	43	VII	Mild	37	0.1	150/110	35	3	39
11	43	XI	Essential hypertension	34	0 6	160/110	33	6	39
12	[illegible]	I	Subacute nephritis	39	0.8	140/100	24	4	40
13	33	V	Chronic pyelonephritis	36	2.2	130/90		5	39

RESULTS

The ocular fundus findings provided by both ophthalmoscopy and fluorescein angiography were first assessed by the conventional criteria and subsequently independently on the basis of the A/V ratio.

Using the conventional criteria, ophthalmoscopy showed that all the 10 healthy non-pregnant women had normal ocular fundi, as did 5 of the 11 normal pregnant women whereas the remaining 6 had angiospastic changes of varying degree, even to the extent of haemorrhage and papilloedema Two of the 13 toxaemic patients had normal ocular fundi (cases 3 and 9 Table I), while the remaining 11 had hypertensive changes of varying degree in the ocular fundi 3 had papilloedema (cases 1 6 and 7).

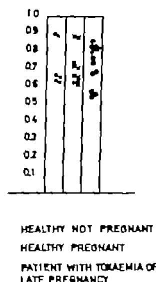


Fig 1 Artery/ ein (A V) ratios f the groups examined, calculated from fluorescein angiography photographs. ■ Healthy not pregnant healthy pragnant, O patient with toxaemia f late pregnancy

Adopting conventional criteria, fluorescein angiography also revealed that of the 11 healthy pregnant women, 4 had normal ocular fundi as in ophthalmoscopy whereas in 1 case which was normal on ophthalmoscopy angiography revealed definite focal arteriolar spasms.

The vasospastic changes in the remaining 6 ocular fundi were easier to detect by angiography while the papilloedema could not be detected by this method. In the toxaemic series, one patient (case 9) had a perfectly normal ocular fundus while the others had spastic changes. Diffuse fluctuations in calibre and pronounced local spasms were the most common of these changes. Three patients (cases 5 8 and 10) had retinal haemorrhages.

The A/V ratio of the fundal vessels should reveal any possible spasticity of the arteries. The ratio was determined on the basis of photography of the ocular fundus. Conventional photography revealed nothing remarkable compared with the results of angiography hence it was not con-

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ULTRASTRUCTURE OF A GRANULOSA CELL TUMOUR

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Abstract. The fine structure of a hormonal active granulosa cell tumour is described. The greater part of the tumour consisted of a cell type resembling the granulosa cell of the normal follicle. It contained many Golgi elements but was poor in smooth and rough endoplasmic reticulum. Another type of cell was found in the proximity of strands of connective tissue. The second type had large amounts of smooth endoplasmic reticulum and lipid droplets. This type is probably the thecal element and its ultrastructure indicates that it represents the endocrine active part of the tumour.

The incidence of ovarian tumours with hormonal activity is relatively low. Therefore the publications on the fine structure of these tumours are few. Green & Maqueo (1966) described the electron microscopy of an androgen producing hilar cell tumour. Two granulosa cell tumours have been studied (MacAulay et al., 1967, Toker 1968). In these two tumours only one cell type was described. Both tumours seemed to have been hormone producing, but surprisingly the cells did not show the ultrastructural characteristics of steroid producing tissue. For some years we have been studying the fine structure of the endocrine active cells of the human ovary (Pedersen & Larsen, 1968 and unpublished data). As we found controversy between the ultrastructure of the previously described granulosa cell tumours and their hormonal activity we felt it worthwhile to investigate an example of this rare tumour.

MATERIAL AND METHODS

The tumour was obtained from a 51-year-old woman who had metrorrhagia [illegible] years after the menopause.

The tumour was cut into pieces of less than 1 mm³ and within few minutes fixed with [illegible]% osmium tetroxide in buffered s-collidine buffer. The fixative was made hypotonic with sucrose and two drops of 1% calcium chloride were added to every 15 ml fixative. The tissue was fixed for 2 hours, dehydrated through increasing concentrations of ethanol and embedded in DOW-epon® (Lockwood, 1964). Ultra-thin sections were cut on LKB- and Porter-Blum ultramicrotomes. The sections were stained with lead citrate and uranyl acetate and examined in a JEM-6C electron microscope. One micron thick sections from the epon blocks were used for light microscopic observations after staining with 1% toluidin blue. In addition tissue was fixed with Bouin's solution, embedded in paraffin and stained with hematoxylin and eosin for light microscopy.

RESULTS

The tumour was found in the left ovary and measured 6 cm in diameter. The uterus was slightly enlarged and the endometrium showed irregular hyperplasia but no indication of progestational influence.

Light microscopy

In sections from the left ovary the normal tissue was displaced by the tumour. The neoplastic tissue appeared very loose because of the abundance of cells and the scarcity of intercellular substance. Most of the tumour consisted of a single type of cell arranged in a trabecular pattern and few rosettes (Fig. 1). These cells were uniform in size and shape resembling the granulosa cell of the normal follicle. They were polygonal and measured about 10–15 μ in diameter. The cells of the rosettes were columnar with their long axis radiating from the centre of the rosette. Some of the rosettes contained a small vessel.

Trabeculae of connective tissue with vessels penetrated into groups of these cells and in the connective tissue another type of cell was observed (Fig. 2). Most cells of the second type were

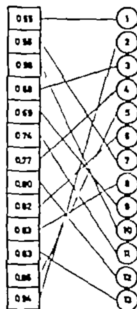


Fig 3 The toxaemic patients, on the left, arranged according to their A/V ratios, with the most spastic arteries at the top. On the right, the same patients are arranged according to their clinical conditions, the most severe at the top. Figures refer to patients in Table I. Lines are drawn to indicate the patient to whom the value belongs.

rather subjective order according to the ophthalmologic appraisal and the clinical status of toxaemia, the correlation did not appear appreciably better

DISCUSSION

From a comparison of the different methods of examination, ophthalmoscopy is found to have an advantage in that it provides an overall picture of the eye and allows diagnosis of an existing papilloedema. Neither conventional photography nor angiography provide these advantages. If the period of observation in angiography is extended the papilloedema can also be detected by this method (Jütte & Lemke 1968).

Angiography has the advantage of accurate visualization of the vascular contours consequently demonstration of spasticity is very much more reliable than by ophthalmoscopy or conventional photography The present authors find that an overall impression of the ocular fundus requires simultaneous use of angiography and ophthalmoscopy

Comparison of the groups, surprisingly reveals a variation in the A/V ratio of the healthy non-pregnant women similar to that in the healthy pregnant women and in the toxaemic patients. It would seem, however that if the A/V ratio is considered a yardstick of spasticity the ocular fundus A/V ratio does not permit conclusions such as the measurement of uterine artery calibre in pelvic arteriography the diminution of the diameter of the uterine artery has been found to correlate with the degree of severity of toxaemia (Pystynen et al. 1966)

The study of the ocular fundus findings other than the A/V ratio revealed, as could be expected, that all the findings to be interpreted as pathological in the patients of the other groups were absent from the healthy non pregnant women. A striking observation was that some of the healthy pregnant women showed normal ocular fundus findings while others showed changes to be interpreted as markedly pathological one of these later developed mild toxaemia. On the other hand, it has already been reported that the toxaemic patients may show perfectly normal ocular fundi, a finding which agrees with the present results.

On the basis of the above observations it would seem that no particularly farreaching conclusions concerning the nature of the toxaemia can be drawn from an individual examination of the ocular fundus.

REFERENCES

Duke-Elder, S., System of Ophthalmology Kimpton, London. Vol. X 350, 1967
von Graefe, A., v Grefes Arch Ophthal 2 I, 222, 1855
Hollwich, F Ber Deutsch Ophthal Ges 63 117 1960.
— Zbl Gynäk 83 415 1961
Jütte, A. & Lemke, L. Intravitalfärbung am Augenhintergrund mit Fluorescein-Natrium. Enke Stuttgart 1968 Beih. Klin. Mbl. Augenheilk., H. 49
Kyrieleis, W Geburtsh u Frauenheilk 14 869 1954
Landesman, R., Douglas, G. & Snyder S. Amer J Obstet Gynec 62 1020, 1951
— Amer J Obstet Gynec 63 16, 1952.
Mittelstrass, H. & Wolfhagen, O Geburtsh u Frauenheilk 8 671 1948.
Novotny H. & Alvis, D Circulation 4 82, 1961.
Pystynen, P Raimo, J Vouttilainen, A., Rytöll, A. & Järvinen, P A. Acta Obstet Gynec Scand 45 Suppl. 9 86, 1966.
Werkö, L. Nord Med 40 1857 1948

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spindle shaped but polygonal cells were also found. They were slightly larger than the first type and many cells contained osmiophilic granules.

Electron microscopy

The *first type of cell* (Figs. 3, 4 and 6) was scattered in a loose intercellular substance containing few collagenous fibrils. Only the cells arranged in rosettes with a central vessel were preserved satisfactorily. A short distance from the vessels the cell membranes were discontinued and the cytoplasm showed large empty areas, as a sign of necrosis or poor fixation. When arranged in rosettes or trabeculae the cells were connected with desmosomes.

The nuclei were small, rather homogeneous and regular with few indentations. Intranuclear areas of low electron density were often observed (Fig. 5).

The mitochondria were numerous. They contained few cristae and some had osmiophilic inclusions. Tubular mitochondria were not observed. The most conspicuous organelle was the Golgi apparatus many of which were present in every cell. The cytoplasm was poor in rough endoplasmic reticulum and free ribosomes. Smooth endoplasmic reticulum was present in some of the cells of the rosettes but never in large amount. Centrioles were often found. Parts of the cytoplasm contained no other organelle than a thread-like structure (Figs. 5 and 6). These fibrils had a diameter of about 50 Å. They were scattered around in the cytoplasm without any relation to other organelles. Multivesicular bodies were present in many cells and they were often found in the vicinity of the Golgi apparatus. Lipid droplets were present in many cells. Lysosomes were rare.

The *second type of cell* was of the same size or little larger than the first type. The most important difference in the ultrastructure of the two types was the abundance of smooth endoplasmic reticulum in the second type (Figs. 7 and 8). In some of these cells most of the cytoplasm was occupied by large droplets of medium electron dense material surrounded by accumulations of smooth endoplasmic reticulum. The smooth endoplasmic reticulum was arranged in multilamellated structures in some of the cells (Fig. 8) but most often it was found in the form of short irregular tubules and vesicles (Fig. 7). These cells did not contain fibrils. The mitochondria and the rough endoplasmic reticulum did not differ from those of the first type.

The *endothelial cell* (Figs. 3 and 4) rested on a basement membrane. They contained organelles of the usual type but were very rich in Golgi elements and pinocytotic vesicles. They had many intracellular fibrils. Many osmiophilic inclusions were observed in the endothelial cells (Fig. 4). These inclusions were elongated with their long axis perpendicular to the surface of the endothelial cell. They measured about $0.2 \times 0.5\ \mu$.

The *intercellular substance* contained fibrillar material. Close to the connective tissue this material consisted of collagenous fibrils while the fibrillar material was less characteristic in other areas. The fibrillar substance was condensed around some of the cells, simulating a basement membrane.

DISCUSSION

The ultrastructure of this tumour differed from the two previously described granulosa cell tumours. Both MacAulay et al. (1967) and Toker (1968) found in the tumour only one type of cell. MacAulay et al. (1967) described the presence of only small amounts of smooth endoplasmic reticulum. Neither did the cells described by Toker (1968) contain any considerable quantity of this structure.

In the present study two types of cells were observed. The *first type* resembled that described by MacAulay et al. (1967) and Toker (1968) and presumably represents the granulosal element. This type of cell was characterized by little or no smooth endoplasmic reticulum but an abundance of fibrils. These filaments were also observed by Toker (1968) and MacAulay *et al.* (1967). The last authors discuss whether they are fibrils or microtubules, but as osmium tetroxide was used as the only fixative in their study it is doubtful whether microtubules would have been preserved. The fibrils found in the cytoplasm in the proximity of the desmosomes had an identical appearance to the tonofibrils of the desmosomes. Cytoplasmic fibrils have been observed in testicular interstitial cells of bird (Fawcett & Burgos, 1960). These cells are specialized for production of steroids, but intracellular fibrils are not characteristic for steroid producing cells and were not observed in human granulosa (Pedersen & Lar-

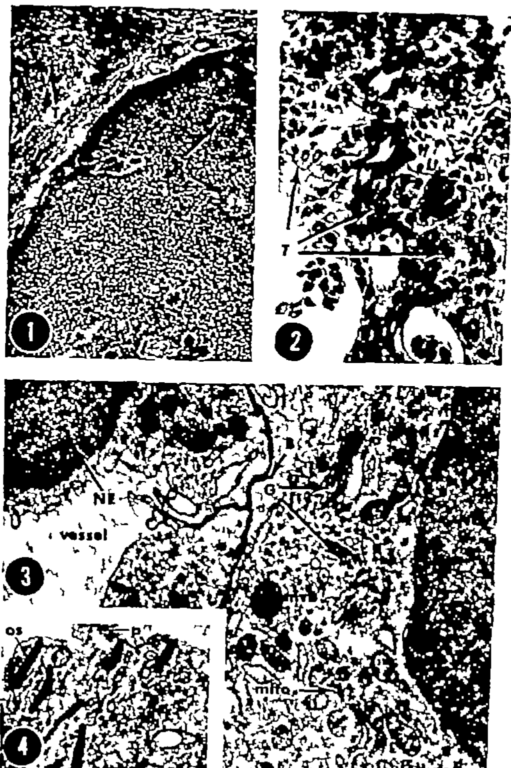


Fig 1 Light micrograph. Portion f tumour with a large accumulation of type-I cells, some f which are arranged as rosettes (*R*) containing a small essel. The other type of cell (*T*) is found in the connectiv tissue. 108.

Fig Light micrograph. Section from epon-embedded material showing connectiv tissue with essels and type-II cells (*T*) Note the acuolated cytoplasm of these cells. Toluidine blue 770

Fig 3 Portions of tw endothelial cells and a type-I cell f a rosette The cells are in close contact but separated by the basement membrane (*B*) f the endothelium. The perivascular cell contains extensiv Golgi material (*G*) and multivesicular bodies (*mvb*). *NE* nucleus of endothelial cell, *NG* nucleus of type I cell, *mito* mitochondria. 13 500.

Fig 4 Luminal part of an endothelial cell in rosette osmiophilic granule *p* pinocytotic esicles 15,300

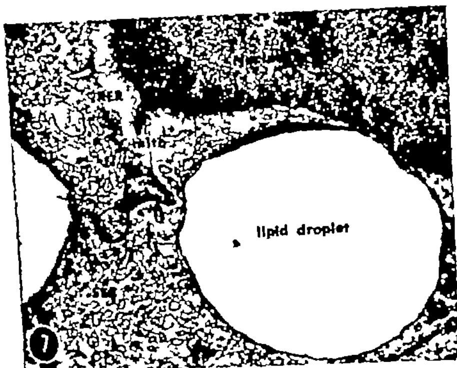




Fig. [illegible] Portion of type-II cell. Note the abundance [illegible] smooth endoplasmic reticulum (SER) and the large lipid droplets. RER rough endoplasmic reticulum. 17 100

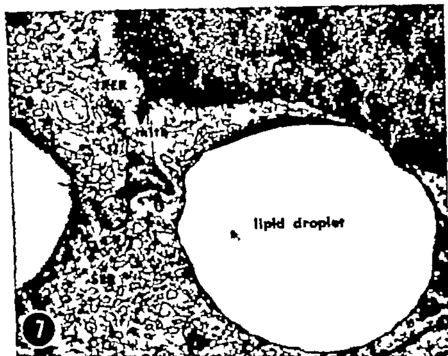
Fig. 8. Multilamellar structure formed by concentrically arranged elements of the smooth endoplasmic reticulum in [illegible] type-II cell. mito mitochondrion. 31 [illegible]00





Fig 5 Portion f type I cell. The white arrow indicates an intranuclear area with low concentration of chromatin. Note the intracellular fibrils, *rer* rough endoplasmic reticulum, *mito* mitochondria. 20,000

Fig 6 Portion f type-I cell Note the abundance of fibrillar material and Golgi elements *mito* mitochondria, *cent* centriole. 15,200.



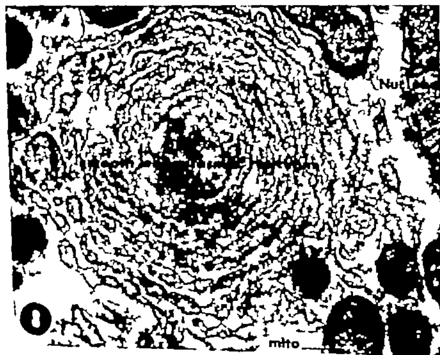


Fig. 7. Portion of type-II cell. Note the abundance of smooth endoplasmic reticulum (SER) and the large lipid droplets. RER rough endoplasmic reticulum. 17,100.

Fig. 8. Multilaminated structure formed by concentrically arranged elements of the smooth endoplasmic reticulum in a type-II cell near mitochondrion. 31,500.

sen 1968) or theca lutein cells (unpublished data) when they were fixed with osmium tetroxide alone, but were present in tissue prefixed with glutaraldehyde In the human testis similar fibrils have been described in immature Leydig c lls but were very few or absent in the mature form (Fawcett & Burgos, 1960) The significance of the fibrils is totally unknown

The cells at some distance from the rosettes showed rupture of the cell membrane and empty spaces in the cytoplasm. These changes may be evidence of necrosis caused by anoxia due to an increasing distance between the vessels and the individual cells of the fast growing tumour An other explanation is that the loose tissue has been damaged during the operation and fixation.

The *second cell type* was found in strands of connective tissue carrying vessels to the tumour It contained large amounts of smooth endoplasmic reticulum and lipid droplets. They may be either luteinized granulosa cells or cells of thecal origin No single cytoplasmic element permits distinction between granulosa and theca lutein cells (un published data) The most important difference is the size of the cells. Both types of human lutein cells are rich in lipids and smooth endoplasmic reticulum and contain villous mitochondria with tubular elements. True tubular mitochondria are rare Rough endoplasmic reticulum is present in both types of cells However under the light microscope the second cell-type of the tumour resembled the theca cells by their size and localization in the connective tissue. Moreover the absence of progestational influence on the endometrium in this patient indicates that luteinization had not taken place

The smooth endoplasmic reticulum is the most characteristic cytoplasmic organelle of the normal steroid-producing cell This has been demonstrated during studies of the human granulosa lutein cell (Pedersen & Larsen 1968) the human theca lutein cell (unpublished data) the cells of the human adrenal cortex (Long & Jones 1967) and the interstitial cells of the human testis (Fawcett & Burgos, 1960) Therefore it is probable that the endocrine-active cell of the actual tumour is the second type, which possibly is of thecal origin Analogically the androgen-producing hilar cell tumour described by Green & Maqueo (1966) contained large amounts of smooth endoplasmic reticulum.

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REFERENCES

Fawcett, D W & Burgos, M. H., Amer J Anat *107* 45 1960.

Green, J A. & Maqueo, M., Amer J Obstet Gynec *95* 478 1966.

MacAulay M. A., Weliky I & Schulz, R. A Lab Invest *17* 56_, 1967

Lockwood, W R., Anat Rec *150* 129 1964.

Long, J A. & Jones, A. L. Lab Invest *17* 355 1967

Pedersen, P H. & Larsen, J F Acta endocr (Kbh) *58* 581 1968.

Toker C., Amer J Obstet Gynec *100* 388, 1968

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AN INSTRUMENT TO AID LAPAROSCOPIC DIAGNOSIS

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Abstract A description is given of a new device constructed to aid laparoscopic diagnosis. The instrument functions as an organ-forceps to be inserted into the abdominal cavity during laparoscopy enabling the pelvic organs to be lifted up and examined more closely

Laparoscopy is a method of examination which has become indispensable in gynaecology Not only gynaecologists but also surgeons and physicians can benefit from it. With the instrument the whole abdominal cavity from the pouch of Douglas to the diaphragm can be surveyed and the majority of the structures within the abdominal cavity can be inspected By means of the laparoscope biopsies can be performed under direct vision (Samuelsson & Sjöstedt, 1961)

To simplify the examination and get as much information as possible, one can use various instruments as aid. With a clamp applied to the anterior lip of the cervix an assistant can move the uterus and improve the view for the operator An instrument for hysterosalpingography inserted before the laparoscopy can give valuable information about the tubal patency

When observing the pelvic organs, sometimes it can be difficult to examine all the details, as the organs are often concealed by intestinal loops. In order to overcome this difficulty an instrument was devised to lift up the tissues during laparoscopic examination.

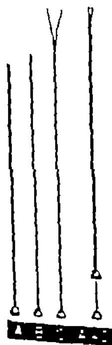


Fig. 1 A Cannula, B Trocar C Organ forceps, A–C Organ forceps in use

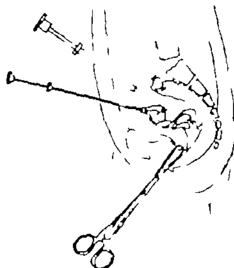


Fig. 2 Schematic view of the instrument in use during laparoscopy

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REFERENCES

Fawcett, D W & Burgos, M. H Amer J Anat *107* 45 1960.

Green, J A. & Maqueo, M. Amer J Obstet Gynec *95* 478 1966.

MacAulay M. A, Weliky I. & Schulz, R. A Lab Invest *17* 562 1967

Lockwood, W R. Anat Rec *150* 129 1964

Long, J A. & Jones, A. L. Lab Invest *17* 355 1967

Pedersen, P H. & Larsen, J F. Acta endocr (Kbh.) 58 581 1968.

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Abstract. A description is given of a new device constructed to aid laparoscopic diagnosis. The instrument functions as an organ-forceps to be inserted into the abdominal cavity during laparoscopy enabling the pelvic organs to be lifted up and examined more closely.

Laparoscopy is a method of examination which has become indispensable in gynaecology. Not only gynaecologists but also surgeons and physicians can benefit from it. With the instrument the whole abdominal cavity from the pouch of Douglas to the diaphragm can be surveyed and the majority of the structures within the abdominal cavity can be inspected. By means of the laparoscope biopsies can be performed under direct vision (Samuelsson & Sjöstedt, 1961).

To simplify the examination and get as much information as possible, one can use various instruments as aid. With a clamp applied to the anterior lip of the cervix an assistant can move the uterus and improve the view for the operator. An instrument for hysterosalpingography inserted before the laparoscopy can give valuable information about the tubal patency.

When observing the pelvic organs, sometimes it can be difficult to examine all the details, as the organs are often concealed by intestinal loops. In order to overcome this difficulty an instrument was devised to lift up the tissues during laparoscopic examination.

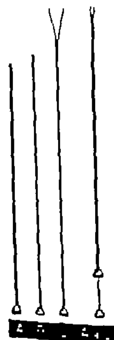


Fig. 1. A Cannula, B Trocar, C Organ forceps, A + C Organ forceps in use.

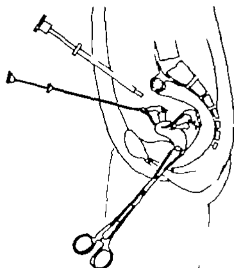


Fig. 2. Schematic view of the instrument in use during laparoscopy.

The new instrument (Fig. 1) consists of a steel pin, forked at one end, which is inserted through a trocar-cannula, the forceps points, when withdrawn into the cannula, close on the organ that can then be lifted and examined more closely (Fig 2)

Laparoscopy is preferably performed under general anaesthesia. Carbon dioxide is used for insufflation of the peritoneal cavity The skin incision is made in the midline below the umbilicus. When the laparoscope is inserted and the abdominal cavity is inspected the organ forceps are introduced a few cm to the right of and below the laparoscope. When inserting the instrument a small puncture-incision is made in the skin. To avoid injuries to the epigastric vessels, the abdominal wall is simultaneously transilluminated by aid of the laparoscope. When the trocar-cannula and stylet are inserted, the stylet is exchanged for the organ forceps.

The organ forceps are a great help in the examination of patients suffering from sterility when it is necessary to find out if the tube is attached to the ovary or peritoneum by adhesions which reduce its mobility and consequently interrupt its function Such small adhesions may be difficult to discover unless, when performing laparoscopy it is possible to lift the tubes and make them fully accessible to inspection

This instrument has been tested at several gynaecological departments in Sweden for some years and has proved to be of great help when performing gynaecological laparoscopy

Mr Karl Bergström, Centrallasarettet, 500 01 Borås, Sweden, will supply the instrument upon request

REFERENCES

Jacobson, L. Laparoscopy in the diagnosis of acute salpingitis Acta obstet gynec scand 43 160 1964

Samuelsson, S. Coeloskopi som gynekologisk undersokningsmetod. Nord Med 63 770 1960.

Samuelsson, S. & Sjöstedt, S. Transperitoneal liver biopsy under peritoneoscopic control. Acta Med Scand 170 627 1961

Sjövall, A. Size-measuring at laparoscopy Acta obstet gynec scand 42 779 1963

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DIE BEDEUTUNG DES FEHLENS EINER ARTERIE IN DER NABELSCHNUR

Eine prospektive endemiologische Studie

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Abstract. In a 5-year delivery series of 19 422 cases lending itself well to epidemiologic studies, the aplasia of one umbilical artery was present in 0.27%. Of these, 32% had other congenital malformations. In those cases, where one umbilical artery was missing without other congenital malformations, there was no increased incidence of prematurity but an increased incidence of low birth weight was present, which, however, was not statistically significant. If the aplasia of the umbilical artery was combined with other congenital malformations, clear prematurity and significant low birth weight were present. The anomaly was equally frequent for primiparae and multiparae. No seasonal variation was found. It is plausible to suggest from some of the cases of this series that both exogenic agents and hereditary factors can cause absence of one umbilical artery.

Das Fehlen einer Arterie in der Nabelschnur wird als die am häufigsten vorkommende Missbildung beim Menschen angesehen (Benirschke & Bourne, 1960) und oft wird sie in Vereinigung mit einer anderen kongenitalen Anomalie angetroffen. In der modernen obstetrischen Literatur wurde auf die Bedeutung dieser Anomalie wiederholt hingewiesen, obwohl man über deren Frequenz in einem obstetrischen Material grösseren Umfanges bisher noch im Unklaren war. Die vorliegende Untersuchung beabsichtigt, die Häufigkeit und Bedeutung des Fehlens einer Nabelschnurarterie aufzuzeigen. Sie wurde in Form einer prospektiven, genauestens planierten, endemiologischen Studie an der obstetrisch-gynäkologischen Klinik der Stadt Malmö in einer 5-Jahresperiode (zwischen 1963–1968) durchgeführt.

MATERIAL UND METHODE

In der Zeit vom 16.2.1963 bis 15.2.1968 wurden an unserer Klinik 19 422 Kinder geboren. Sämtliche lebend und totgeborenen Kinder von der 28. Graviditätswoche ab wurden mitgerechnet. Nach jeder Entbindung wurde die Nabelschnur genauestens untersucht, wobei in Fällen, da drei Nabelschnurgefässe nicht mit Sicherheit identifiziert werden konnten, zwecks Dokumentation eine pathologisch-anatomische Untersuchung vorgenommen wurde. Die klinische Anwendbarkeit eines solchen Vorgehens wurde bereits beschrieben (Little, 1958). Das maternelle Kontrollmaterial zu den Graviditäts- und Entbindungskomplikationen bildeten sämtliche Entbindungen des Jahres 1965. Als Kontrollmaterial zu den Kindern mit Nabelschnuranomalie wurden sämtliche Geschwister (52 Kinder) zu eben diesen Kindern ausersehen. Es zeigte sich nämlich, dass diese beiden Serien sowohl sozial- wie parität-mässig durchaus vergleichbar waren. Die vorliegenden Fälle erscheinen besonders zu einer statistischen Bearbeitung geeignet und sind vor allem deshalb interessant, da sämtliche Entbindungen der Stadt Malmö mit rund einer Viertelmillion Einwohnern an unserer Klinik stattfinden.

RESULTATE

Insgesamt wurden 19 442 Kinder geboren. Davon wiesen 53 Kinder eine Aplasie einer Nabelschnurarterie auf (32 Knaben und 21 Mädchen), was einer Frequenz von 0,27 % entspricht. Von diesen 53 Kindern hatten 17, d.h. 32 %, ein oder mehrere sofort feststellbare körperliche Anomalien. Das durchschnittliche Geburtsgewicht für die 32 betroffenen Knaben war 3 019 g und für die 17 betroffenen Mädchen 2 746 g. Zusammengenommen betrug das durchschnittliche Geburtsgewicht 2 911 g. In der Gruppe der Kinder mit Nabelschnuraplasie ohne sonstige körperliche Anomalie betrug das Durchschnittsgewicht der Knaben 3 403 g und das der Mädchen 947 g. In der Gruppe, in der die Nabelschnuraplasie in Vereinigung mit einer anderen körperlicher Anomalie

Table I *Fehlen einer Nabelschnurarterie in Bezug auf das mütterliche Alter und die mütterliche Parität*

Alter	–20	20–34	35–	Total
Primiparae	5	1	1	27
Multiparae	1	1	4	26
Total	6	42	5	53

Table II *Anzahl der Fälle mit Nabelschnuranomalie aufgeteilt auf die verschiedenen Monate (5 Jahresperiode)*

Monat für die letzte Regel	Totalanzahl der Entbindungen	Fehlen einer Nabelschnurarterie	
		Anzahl	
Januar	1 543	1	0,06
Februar	1 707	7	0,41
März	1 8 6	3	0,16
April	1 8 7	6	0,33
Mai	1 8_3	6	0,33
Juni	1 589	4	0_5
Juli	1 593	3	0,19
August	1 515	4	0,26
September	1 53	6	0,39
Oktober	1 495	6	0 40
November	1 459	4	0,27
Dezember	1 513	3	0,20
Summa	19 4_	53	0_7

auftrat betrug das Durchschnittsgewicht der Knaben 1 865 g und das der Mädchen 2 478 g.

Die Anzahl Aplasiefälle einer Nabelschnurarterie wurde zum mütterlichen Alter und zur mütterlichen Parität in Relation gesetzt, was aus Tabelle I hervorgeht. Das Material wurde ausserdem in Beziehung zur saisonmässigen Verteilung der Monate für die letzte Regel studiert, wie es in der Tabelle II dargestellt wird. Ausserdem wurde Rücksicht auf die während der Gravidität beobachtete toxische Hypertonie und Hydramnion sowie eine totale Plazentarretention nach der Geburt genommen, siehe Tabelle III. Aus Tabelle IV wird die Art der Missbildungen ersichtlich, die bei den Kindern mit nur zwei Nabelschnurarterien gefunden wurde. Aus Interessensgründen wurde schliesslich eine Zusammenstellung früher publizierter prospektiver Untersuchungsserien in Tabelle V aufgestellt.

DISKUSSION

Bereits 1870 beschrieb Hyrtl 1_ Fälle bei denen eine Umbilikalarterie fehlte, von denen bei _ Fällen ausserdem schwere Missbildungen vorlagen. Seinen Beobachtung wurde aber lange kein weiteres Interesse geschenkt. Erst im Jahre 1955 wurde von Benirschke und Brown eine retrospektive Studie von 55 Fällen mit Aplasie einer Nabelschnurarterie publiziert, wonach eine Anzahl weiterer Veröffentlichungen erschienen. Daher ist es unsicher ob diese Anomalie erst in den letzten Jahrzehnten häufiger als früher auftritt, oder ob das regere Interesse für diese eine höhere Frequenz in der letzten Zeit vorspiegelt. Im Hinblick darauf wird die Forderung nach einer prospektiv angelegten Studie aus einem grösseren einheitlichen Entbindungsmaterial notwendig, um die klinische Bedeutung dieser Anomalie erfassen zu können.

In früher publizierten Serien (Tabelle V) wurde die Anomalie durchschnittlich in 0,61 (0,10–1,11) nachgewiesen. In der vorliegenden Untersuchung beträgt die entsprechende Ziffer 0,_7 %. Die Serien früherer prospektiver Untersuchungen sind aber uneinheitlich und dadurch nicht repräsentativ, wodurch ein Gegenüberstellen mit vorliegender Serie nicht möglich ist. So besteht z.B.

Table III *Graviditäts- und Entbindungskomplikationen bei Müttern von Kindern mit Nabelschnuranomalie (53 Fälle) im Vergleich zum Kontrollmaterial (4 010 Fälle)*

Graviditätskomplikationen	Kontrollmaterial		Fehlen einer Nabelschnurarterie	
	Anzahl		Anzahl	
Hypertonia gra	1 7	1_	5	9 4
Hydramnion	6	0 1	4	7 8
Retentio placentae tot.	45	1_	4	7 8

Table IV *Auftreten anderer körperlicher Missbildungen bei Kindern mit Aplasie einer Nabelschnurarterie*

Organsysteme	Anzahl der Fälle	Anzahl der Missbildungen
Skelettsystem	6	9
Digestionskanal	5	8
Urogenitalsystem	5	16
Herz und Kreislauf		
Respiratorisches System		
Zentrales Nervensystem	6	6
Übrige Missbildungen	5	5

das 1966 von Froehlich und Fujikura publizierte Material aus Fällen von 12 verschiedenen Kliniken, zwei andere publizierte Materialien umfassen Weisse und Neger (Peckham, und Yerushalmy 1965 Froehlich und Fujikura, 1966) Soweit ermessen werden kann, bestehen keine derartigen Mängel im vorliegenden Material, das aus einem sehr begrenzten Aufnahmegebiet mit einer homogenen B-völkerung stammt.

Es besteht die Auffassung, dass das Geburtsgewicht on Kindern mit nur einer N belschnurarterie im Vergleich zu Kindern mit normalen Gefässen in der Nabelschnur niedriger liegt, wenn auf die Lange der Gravidität Rücksicht genommen wird (Bourne und Benirschke, 1960· Peckham und Yerushalmy 1965 Cipparone, 1966). Derartige Neugeborene werden daher oft als „prämatur" betrachtet, was aber in Wirklichkeit gar nicht zutrifft (Seki und Strauss, 1964). Der Prozentsatz von kongenitalen körperlichen Missbildungen bei Nabelschnuranomalie liegt in den Materialien zwischen 10 und 58 Prozent, die Missbildungen können dabei die meisten Organe und Organsysteme des Körpers betreffen. Man konnte z.B bei Urographie von klinisch normalen Kindern mit nur 2 Nabelschnurgefässen in 30% pathologische Pyelogramme feststellen (Feingold, Fine und Ingall, 1964) In einer späteren Untersuchung konnten derartige Befunde nicht mehr erhoben werden (Van Leeuwen, Behrinnger und Glenn, 1967).

Bei der statistischen Bearbeitung vorliegender Serie kam der U Test nach Mann-Whitney zur Anwendung Dabei wurde gefunden, dass das Geburtsgewicht von Kindern mit nu zwei Nabelschnurgefässen hochsignifikant niedriger war als das der Kinder des Kontrollmaterials. Verglich man mit dem Kontrollmaterial aber das Material der Nabelschnuranomalien ohne weitere Korpermissbildungen, konnte nur eine Tendenz zu einem niedrigeren Gewicht, aber kein sicherer Gewichtsunterschied festgestellt werden. Ein hochsignifikanter Gewichtsunterschied lag auch zwischen Kindern mit und Kindern ohne korperliche Missbildung vor Man kann also konstatieren, dass die Aplasie einer Nabelschnurarterie an und für sich keine Senkung des Geburtsgewichtes nach sich zieht, dagegen wohl eine erhöhte Neigung zu kongenitalen korperlichen Missbildungen, welche ihrerseits dann das Geburtsgewicht senken. Ebenso zeigte sich im Material der Nur Nabelschnuranomalien keine Tendenz zu Prämaturität, wohl aber dann, wenn noch andere Missbildungen gefunden wurden

Table V *Zusammenstellung publizierter prospektiver Untersuchungsserien über Fälle on Nabelschnuranomalie*

Autor	Jahr	Anzahl der Entbindungen	Fälle mit Aplasie einer Nabelschnurarterie	
			Anzahl	%
Benirschke & Bourne	1960	1 500	15	1,00
Lyon	1960	717	8	1 11
Little	1961	2 800	21	0 75
Thomas	1961	6 970	27	0,39
Järvinen et al	1962	3 100	15	0 48
Lenoski & Medovy	1962	2 500	5	0,20
Adler et al	1963	2 900	19	0,95
Cairns & McKee	1964	2 000	20	1,00
Feingold et al.	1964	6 000	32	0,53
Fujikura	1964	5 9[illegible]	38	0,64
Gönczi & Koller jr	1964	1 000	8	0,80
Bourquel	1965	3 000	3	0,10
Kristoffersen	1965	4 400	16	0,36
Papadatos & Paschos	1965	7 8[illegible]	32	0,41
Peckham & Yerushalmy	1965	5 8[illegible]	51	0,87
Adrian	1966	3 6[illegible]	23	0,68
Ampolillo & Pascucelli	1966	1 500	3	0,20
Froehlich & Fujikura	1966	26 339	703	0 76
Van Leeuwen et al	1967	2 000	6	0,30
Total		89 500	547	0,61
Eigenes Material		19 422	53	0,27

Interessanterweise konnte festgestellt werden dass Nabelschnuranomalien bei Weissen häufiger vorkamen als bei Negern (Peckham und Yerushalmy 1965 Froehlich und Fujikura, 1966), wogegen das Auftreten dieser Anomalie bei Negern mit einer grösseren Frequenz anderer Körpermissbildungen verbunden war

Was die Verteilung der Geschlechter betrifft, liegen bisher widerspruchsvolle Resultate vor In einem Material waren Knaben häufiger von der Anomalie betroffen (Hyrtl, *1870*), im einem anderen Mädchen (Adler Lewenthal und Ben-Aderet, 1963). In zwei weiteren Serien wurden keine Geschlechtsunterschiede festgestellt (Little, 1958 Peckham und Yerushalmy 1965). Im vorliegenden Material berwiegen wohl die Knaben an Haufigkeit, der Unterschied Knaben/Mädchen im Vergleich zur Kontrollgruppe konnte aber statistisch nicht sichergestellt werden.

Es zeigte sich in einigen Materialien dass Nabelschnuranomalie häufiger bei Kindern von Erstgebärenden als bei Mehrgebärenden auftrat (Bourne und Benirschke 1960) In anderen Materialien konnte ein solches Resultat nicht gefunden werden (Järvinen, Österlund und v. Numers, 1962 Froehlich und Fujikura, 1966) Ebenso konnte in der vorliegenden Serie kein derartiger Unterschied festgestellt werden. Auch hatte das mütterliche Alter keinen Einfluss auf die Häufigkeit dieser Anomalie, sowie auf die Anomalie in Verbindung mit weiteren Missbildungen

Was den Zusammenhang dieser Anomalie mit anderen Komplikationen und Krankheiten betrifft, wurden teils erhöhte Präeklampsiefrequenz (Benirschke und Brown, 1955 Kristoffersen, 1965 Peckham und Yerushalmy 1965) teils vermehrtes Auftreten von ante partum Blutungen (Bourne und Benirsche 1960) teils auch erhöhte Frequenz von Diabetes mellitus (Froehlich und Fujikura, 1966) von mütterlicher Seite benannt. In einer anderen Untersuchungsserie wurde im Gegensatz dazu keine erhöhte Frequenz dieser Zustände angegeben (Little, 1961) Was die vorliegende Serie betrifft konnte eine gewisse Tendenz zu vermehrt auftretenden Hydramnion, Graviditätshypertonie und totaler Plazentarretention beobachtet werden, das Material reichte aber nicht zur statistischen Bearbeitung dieser Details.

Eine hereditäre Ursache für das Fehlen einer Nabelschnurarterie wurde bisher verneint (Bourne und Benirschke 1960 Sullivan und Marin-Padilla, 1964 Seki und Strauss 1964) auf der anderen Seite wurde aber die Anomalie oft bei autosomaler Trisomie beobachtet (Uchida, Bowman und Wang, 1962) was auf zu Grunde liegende Chromosomdefekte hindeuten könnte. Bei Zwillingen wurde die Anomalie in erhöhtem Ausmasse mitgeteilt (Bourne und Benirschke, 1960) Wider Erwarten fand man aber dass bei 125 Zwillingspaaren wohl 17 Einzelkinder diese Anomalie hatten unter ihnen aber nur ein einziges Zwillingspaar und das waren interessanterweise zweieiige Zwillinge (Benirschke, Sullivan und Marin-Padilla, 1964) Das Vorkommen der Anomalie bei ein und derselben Mutter bei zwei aufeinander folgenden Graviditäten wurde beschrieben (Adler Lewenthal und Ben-Adereth 1963) Ein solcher mütterlicher Fall kommt auch in der vorliegenden Serie vor was natürlich die hereditäre Theorie etwas unterstützt dies macht auch ein anderer Fall des Materials der mit dem Uterus duplex und der Aplasie der einen Niere. Dabei ist ganz interessant, dass gerade Nierenaplasie eine nicht ungewöhnliche Missbildung bei Nabelschnuranomalie ist, wie es in Tabelle IV angedeutet wird. Nur ein Fall von mütterlichen Diabetes mellitus kommt in der vorliegenden Serie vor

Im Allgemeinen ist die Ansicht verbreitet, dass Aplasie einer Nabelschnurarterie von exogenen Noxen hervorgerufen wird (Thomas, 1963). So wurde die Anomalie bei Thalidomid Embryopathie beschrieben (Thomas, 1963) In einem Falle unseres Materials hatte eine Mutter in der Frühgravidität eine Zervicitis, hervorgerufen durch den Herpes simplex Virus, wobei das Kind mit Nabelschnuranomalie + Hydrocephalus, Agenesie beider Nieren und Phokomelie sowie anderen Missbildungen geboren wurde Dieser Fall ist deswegen besonders interessant, weil man weiss, dass der Herpes simplex Virus in der Gewebekultur in einer hohen Frequenz Chromosomenaberrationen hervorruft und daher auch verdächtigt ist, Missbildungen hervorzurufen (Cederqvist, Eliasson und Lindell, 1967)

In einem Material wurde eine saisonmässige Variation gefunden, und zwar wurde bei Müttern mit der letzten Regel zwischen Juli und September Nabelschnuranomalien in doppelt so hoher Frequenz festgestellt wie in den übrigen Monaten (Peckham und Yerushalmy 1965) Die statistische Bearbeitung unseres Materials ergab keine Anhaltspunkte für eine solche saisonmässige Variation.

ZUSAMMENFASSUNG

I einem homogenen Entbindungsmaterial on 19 422 Fällen (5-Jahresperiode), das für endemiologische Studien geeignet erscheint, wurde in einer prospektiv angelegten Untersuchung das Fehlen einer Nabelschnurarterie bei 0.27 festgestellt. 32 dieser Fälle hatten gleichzeitig auch andere körperliche Missbildungen. In Fällen, bei denen nur Nabelschnuranomalie ohne ander Missbildung gegeben war lag keine Tendenz zur Prämaturität vor wohl aber eine Tendenz zu herabgesetztem Geburtsgewicht, ohne dass diese Herabsetzung signifikant ar War Nabelschnuranomalie vereinigt mit einer anderen körperlichen Missbildung, lag ausgesprochene Pr maturität und signifikant herabgesetztes Geburtsgewicht or Die Anomalie trat bei Erst und Mehrgebärenden ungefähr gleichoft auf, ebenso konnte keine Jahreszeitliche Abhängigkeit nachgewiesen werden. Einige Fälle des Materials deuten darauf hin, dass sowohl exogene Noxen wie hereditäre Faktoren der Anomalie zu Grunde liegen können.

LITERATUR

Adler, J., Lewenthal, H. & Ben-Adereth, N. Harefuah 65 218, 1963.

Adrian, K. Aplasi av navelsträngsartär. Obstetrik & Gynekologi 3. Berlingska Boktryckeriet, Lund, 1966.

Angelillo, M. & Pacinelli, M. L. Riv Ital Ginec 50 478, 1966.

Benirschke, K. & Bourne, G. L. Am J Obstet Gynec 79 251 1960.

Benirschke, K. & Brown, W. H. *Obstet Gynec 6*, 399 1955

Benirschke, K., Sullivan, M. M. & Marin-Padilla, M. Obstet Gynec *24* 819 1964.

Bourne, G. L. & Benirschke, K.: Arch Dis Child *35* 534, 1960.

Bruniquel, M. O. Bull Fed Gynec Obstet Franc *17* 256, 1965.

Cairns, J. D. & McKee, J. Canad M A J *91* 1071 1964

Cederqvist, L., Eliasson, G. & Lindell, L. Brit Med J 3 558, 1967

Capperone, J. A. Amer J Clin Path 45 247 1966.

Feingold, M., Fine, R. N. & Ingall, D. New England J Med 270 1178, 1964

Froehlich, L. A. & Fujikura, T. Am J Obst Gynec 94 274, 1966

Fujikura, T. Am J Obst Gynec 88, 829 1964.

Gombori, Z. & Keller Th. J. Gynec *157* 177 1964.

Hyrtl, J. Die Blutgefässe der menschlichen Nachgeburt. Wilhelm Braumüller Wien, 1870.

Järvinen, P. A., *Österlund*, K. & Numers, C. Duodecim *78* 937 1962.

Kristoffersen, K. Nord Med *73* 89 1965

Lenoski, E. F. & Medovy, H.: Canad M A J *87* 1229 1962

Little, W. A. Bull Sloane Hosp 4 127 1958.

— Obstet Gynec *17* 695, 1961,

Lyon, F. A. Obstet Gynec *16* 719 1960.

Papadatos, C. & *Paschos*, A.: *Obstet Gynec* 26, 367 1965

Peckham, C. H. & Yerushalmy, Y. Obstet Gynec 26 359 1965

Seki, M. & Strauss, L. Arch Path *78* 446, 1964.

Thomas, J. Geburtsh Frauenheilk *21* 984, 1961

— Arch Gynäk *198* 216, 1963

VanLeeuwen, G., Behringer, B. & Glenn, L. J Pediat *71* *103*, 1967

Uchida, I. A., Bowman, J. M. & Wang, H. C. New England J Med 266. 1198, 1962.

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A CASE OF HYDATIDIFORM MOLE WITH SEVERE PREECLAMPSIA AND SEVERE DISTURBANCES IN THYROID FUNCTION

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Abstract A case is reported of hydatidiform mole accompanied by serious degree of toxaemia and severe disturbances in the function of the thyroid gland in a 20-year-old primigravida, who was admitted to the department in the 20th week of pregnancy Clinically the patient showed severe toxaemia with gross oedema, congestion of the lungs, hypertension to approximately 200/130 mm Hg and proteinuria of 4.4 g/1000 ml, but no signs of thyrotoxicosis The toxaemia disappeared after 14 days after treatment by evacuation, blood transfusion, albumin infusion, digitalization, diuretics and antihypertensive agents Eight hours after removal of the mole an extremely high PBI (24 2 μg 100 ml) and low serum cholesterol (97 mg 100 ml) were found. Both of these values returned to normal within the course of 14 days Triiodothyronine uptake on Sephadex G 25 (T_3 test) was found to be 101% and fell simultaneously with the changes in the other values to 48%. I^{131} uptake in the thyroid gland showed increased values 3 weeks after the operation but was normal again 5 weeks later The values for the thyroid function tests which were found are compared with similar values reported in literature and concluded that the changes must be due to the usual effects on thyroid function of normal pregnancy plus an extra factor which must be produced by the molar tissue, and which must either be TSH or some other thyroid stimulator It is recommended that in future TSH activity be determined in plasma and molar tissue in patients with hydatidiform mole and that various thyroid parameters be studied with regard to their possible diagnostic value in cases of hydatidiform mole

Hydatidiform mole occurs in the white population with frequency of approximately 1 per 2500 pregnancies (Novak & Woodruff 1962) and is reported by Greenhill (1960) to be accompanied in about one third of cases by slight toxaemia, but only in rare instances by severe toxaemia.

Since 1960 few publications have appeared reporting considerably increased values for protein bound iodine (PBI) in patients with hydatidiform mole. Dowling et al (1960) found in 3 patients with hydatidiform mole PBI levels of 9.0 13.5 and 20.5 μg/100 ml respectively Felbo & Lund have reported 2 cases with PBI levels of 15 4 and 17 4 μg/100 ml and suggested PBI determinations as an additional diagnostic aid in this condition. Later Kock et al. (1966) published 6 cases with PBI values between 12.1 and 20 0 μg/100 ml and Mann et al (1967) 1 case with a PBI of 17.2 μg/100 ml, Odell et al. (1963) have studied thyroid function in 93 patients with metastatic trophoblastic disease and in 7 patients demonstrated increased thyroid activity with a PBI of from 9 2 to 17.0 μg/100 ml and hypocholesteraemia together with increased radioactive iodine uptake in the thyroid gland. In 4 of the 7 cases thyroid function returned to normal as the neoplasm responded to chemotherapy

Owing to the rare occurrence of hydatidiform mole complicated by severe toxaemia and the unexplained mechanism by which the mole influences thyroid function the following case history is reported.

CASE HISTORY

A 20-year-old, previously healthy primigravida without any family of heart, kidney or metabolic disease, was admitted in the 20th week of pregnancy with history of slight vaginal haemorrhages for the 3 weeks prior to admission and very severe haemorrhage immediately before admission. In the weeks prior to admission she had moderate cough and increasing oedema. Just prior to admission the patient had short period of unconsciousness but no fit had been observed. Because of the vaginal bleeding and slightly increased blood pressure one month before admission immunological HCG determinations had been performed twice, the results were 80,000 and 40,000 units with an interval of 6 days. At that time she was treated as case of threatened abortion with

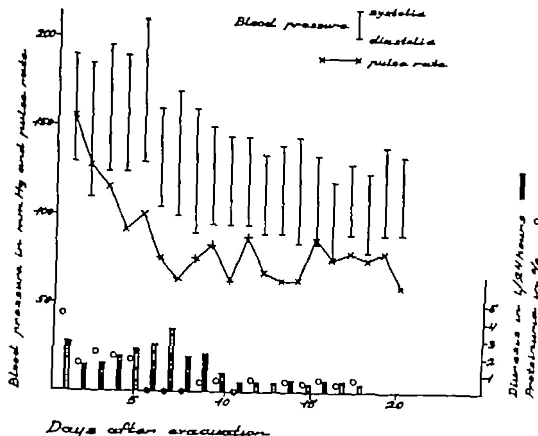


Fig. 1. Blood pressure, pulse rate, urinary output and proteinuria for the 20 days following the removal of the hydatidiform mole.

Allyloestrenolum® (Gestanon). No albuminuria was found at the routine antenatal examinations.

On admission to the gynaecological department the patient was conscious and in pain. She looked very pale but did not appear thyrotoxic. No goitre and no tremor were present, but she had severe generalized oedema. The blood pressure was 150/115 mm Hg, pulse rate 11 /min and there was 4.4 g/1000 ml protein in the urine. The gynaecological examination showed molar tissue in an open cervix with severe haemorrhage, so the uterus as evacuated and 2650 ml of molar tissue and blood were removed. During the operation 1 bottle of Macrodex® and 3 bottles f whole blood were given. Microscopy of the removed tissue showed hydatidiform mole without evidence of malignancy.

In the eight hours after the operation the pulse rate showed a tendency t rise it increased to 160/min at the same time as the blood pressure rose to 200/130 mm Hg. At this time the patient became increasingly dyspnoeic, and X-ray examination of the chest showed an enlarged heart and congestion of both lungs. Digitalization was commenced with Lanatoside C® and later with Digoxin®; antihypertensive treatment consisted of Reserpine® i.m. and Frusemide® also i.m. An albumin infusion wa given because of hypoproteinaemia which as 4.–4.6 g/100 ml. Ophthalmoscopy showed spastic retinal easels without exudates or haemorrhages.



Fig. 2. X-ray of the chest the day following the removal of the hydatidiform mole.

Fig. 1 shows the course of the blood pressure, pulse rate, and urinary output together with the protein excretion in the urine for the first three weeks after the operation. It can be seen that the blood pressure and the pulse rate became normal within 10 days, her weight fell from 83 to 73.6 kg, the haemoglobin concentration increased from 89 g/l t 120 g/l and the serum protein concentration from 4.3 to 8.1 g/100 ml.



Fig. 3. X-ray of the chest 14 days later.

Figs. 2 and 3 show the X-ray pictures of the chest 1 and 14 days after admission, during which time the heart decreased in size and the lung congestion disappeared.

The following tests and examinations performed immediately after the evacuation were all within normal limits: urine microscopy, serum creatinine, blood urea, serum standard bicarbonate, serum sodium, serum chloride, serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase and serum thymol turbidity. The excretion of catecholamines in 24 hour urine were normal. Serum electrophoresis the day after admission showed reduced amount of albumin 2.7 g/100 ml (normal 3.1–4.7) but this returned to normal within 8 days. The electrocardiogram on admission showed inversion of T and this returned to normal with the blood pressure.

Thyroid function tests, protein bound iodine (PBI) triiodothyronine uptake on Sephadex G 25 (T test) and serum cholesterol can be seen in Fig. 4.

I[131] uptake by the thyroid gland three weeks after the operation showed increased values with an uptake of 40 and 86% after 4 and 24 hours respectively. Two months later the same test showed normal values.

The urine excretion of chorionic gonadotrophin measured by the biological method (weight increase of the uterus of infantile rats)* is shown in Table I. The slight increase in the chorionic gonadotrophin excretion 2½ months after evacuation resulted in curettage being per-

* The test was performed by The State Serum Institute, Copenhagen.

Fig. 4. The values of the PBI, T test and serum cholesterol in 8 tests in a period of 3 months following the removal of hydatidiform mole.

Table I *24 hour excretion of chorionic gonadotrophin in 7 determinations within 5 months following removal of a hydatidiform mole*

No of days after removal	24 hour excretion of chorionic gonadotrophin I.u.
2	300,000
19	3 800
53	3,500
85	7 800
98	1 400
114	600
144	Not demonstrated

formed because of a suspicion of chorioncarcinoma. Microscopy of the removed tissue on this occasion showed a proliferating endometrium without signs of malignancy

Oestriol excretion was first determined on the 21st and 22nd day and was 1.3 and less than 1 mg/24 hours (modified chemical analysis according to the method of Brown). These analyses were performed too late to give any information on the production of oestrogen at the time of the original evacuation.

The patient was discharged from the department 25 days after admission completely recovered and no abnormal findings have been demonstrated during outpatient examination upto 12 months after the evacuation.

DISCUSSION

This patient, therefore, had a severe degree of toxaemia associated with a hydatidiform mole. The patient developed hypertension 160/80 a month prior to admission and was subjected to examination for a suspected hydatidiform mole at this time, but the suspicion was considered groundless as falling HCG values (80 000–40 000 units) were demonstrated by immunological tests. It should be noted that a normal HCG excretion does not exclude the diagnosis of hydatidiform mole (Hamburger 1943 Hobson 1958) The ratio between biologically and immunologically determined HCG in the urine (B/I ratio) is often less than 1 with a normal pregnancy and above 1 in the majority of cases of a mole (Wide & Hobson 1967) The use of both methods should thus be of value in the differential diagnosis between a mole and a pregnancy

As also observed in other reports (Kock et al 1966 Mann et al., 1967) our patient did not show the clinical signs of thyrotoxicosis In the first 24 hours in hospital she was restless and talkative and had a tachycardia, but the anaemia, cerebral oedema and the cardial decompensation could quite possibly explain these findings.

The thyroid function tests were first performed some 8 hours after the evacuation. The PBI was at that time 24.2 g/100 ml and fell within the next 4 days to 18 μg/100 ml and became normal within the course of 9 days The serum cholesterol increased simultaneously with the fall of the PBI from 97 to 342 mg/100 ml and the T_3 test fell from 101 to 48% The course of these values suggest a hyperthyroid state at the time of the evacuation, and that this ceased abruptly after the operation so that the values in the following 14 days swing around to show almost hypothyroid levels. The levels on admission exceed those that can be expected with a normal pregnancy where the normal values for PBI are stated to vary from 6.2 to 11.2 μg/100 ml (Heinmann et al 1948) for the T_3 test from 80 to 40% (Kristoffersen & Strange) and for serum cholesterol from 112.5 to 426.5 mg/ml (Documenta Geigy 1960)

The change in the thyroid tests during pregnancy can be explained by the increased oestrogen production which accompanies pregnancy and the changes connected with this in the thyroxine binding globulin (TBG) (Engström & Markardt 1954 Dowling et al., 1956 Engbring & Engström, 1959) Oestrogen production with a hydatidiform mole is however no greater and often less than that occurring during a normal pregnancy (Frandsen & Stakemann 1964 Macnaughton 1965) In addition it differs qualitatively in that the ratio oestriol/oestrone + oestradiol is between 1 and 3 rather than > 10 as in a normal pregnancy The oestrogen production with a mole thus corresponds qualitatively more to the non-pregnant state than the pregnant.

HCG in itself does not appear to influence thyroid function inasmuch as it has not been possible with either a mole (Kock et al 1966) or with choriocarcinoma (Odell et al 1963) to demonstrate a correlation between the HCG titre and the PBI values.

The severely abnormal thyroid function tests found in this case thus cannot be explained as a result of the chorionic gonadotrophin production or the oestrogen production alone It therefore appears permissible, as was suggested by Kock et

The analysis was performed by the Central Laboratory Odense County and City Hospital.

al. (1966) to explain the changes found as a combination of the usual changes in thyroid metabolism caused by a normal pregnancy plus one more factor which is produced in the molar tissue and which is similar to the thyrotrophic hormone or some other thyroid stimulator. The increased I^{131} uptake which accompanied the other changes indicates that the primary factor cannot be either thyroxine or a related hormone.

Unfortunately in the present case we have not been able to study either the serum or the molar tissue for TSH activity. Odell et al. (1963) have found in 2 patients with metastatic trophoblastic disease, with biochemical signs of thyrotoxicosis, a TSH activity in the serum, which was 3–4 times the normal and at the same time a very high activity in the tumour tissue.

On the basis of these findings and the course of the thyroid function tests in the present study it will be of interest in the future to determine the TSH activity in both the plasma and molar tissue in patients suffering from hydatidiform mole together with determinations of the PBI and other thyroid parameters in these patients in order to assess the possible diagnostic value of such tests.

REFERENCES

Documenta Geigy 6th edn. 1960.

Dowling, J. T. Freinkel, N. & Ingbar, S. H. J Clin Endocr 16: 1491, 1956.

Dowling, J. T. Ingbar, S. H. & Freinkel, N.: J Clin Endocr 20: 1, 1960.

Engbring, N. H. & Engström, W. W. J Clin Endocr 19: 783, 1959.

Engström, W. W. & Markardt, B. J Clin Endocr 14: 215, 1954.

Felbo, M. & Lund, J. S. Ugeskr Laeg 126: 1722, 1964.

Frandsen, V. Aa. & Stakemann, G., Acta Endocr (Kbh), Suppl. 90: 81, 1964.

Greenhill, J. P. Obstetrics, 3rd edn., p. 638. W. B. Saunders Co. Philadelphia and London, 1960.

Hamburger, Chr. Acta Obstet Gynec Scand 24: 45, 1943.

Heinemann, M., Johnson, C. E. & Man, E. B. J Clin Invest 27: 91, 1948.

Hobson, B. M.: J Obstet Gynaec Brit Emp 65: 253, 1958.

Koch, H., Kessel, H. Stolte, L. & Leusden, H. J Clin Endocr 26: 1128, 1966.

Kristoffersen, K. & Strange, R.: To be published.

Macnaughton, M. C.: J Obstet Gynaec Brit Comm 72: 249, 1965.

Mann, L. L., Lutz, M. Schulman, H. & Romney, S. L. Amer J Obstet Gynec 98: 1151, 1967.

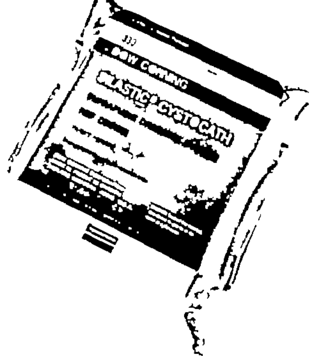
Novak, E. R. & Woodruff, J. D. Gynecologic and Obstetric Pathology. 5th edn., p. 563. W. B. Saunders Co. Philadelphia and London, 1962.

Odell, W. D. Bates, R. W. Rivlin, R. S., Lipsett, M. B. & Hertz, R.: J Clin Endocr 23: 658, 1963.

Wide, L. & Hobson, B. Acta Endocr (Kbh) 54: 105, 1967.

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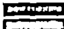
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POST-MENOPAUSAL HYPEROESTROGENISM CAUSED BY CARCINOMA OF THE ADRENAL CORTEX

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Abstract. A case of carcinoma of the adrenal cortex in post-menopausal women is described, in which high excretion of urinary oestrogens, an increased oestrogen activity in vaginal smear and clear oestrogen effect in the endometrium were observed. The possibility that carcinoma in the adrenal cortex may produce oestrogens or their precursors is discussed.

The role of the adrenals as a source of oestrogen in post-menopausal women has been emphasized by many authors (for review see Procopé, 1968). An increased excretion of urinary oestrogen has been observed in patients with adrenal tumours (Slammwhite & Buchwald, 1960) and very high urinary oestrogen values have been noted in patients with carcinoma of the adrenal cortex (Dorfman & Luft, 1952). However adrenal tumours producing androgens and hormonally inactive tumours are more frequent than tumours producing oestrogens.

CASE REPORT

A former shopkeeper aged 72, was admitted on account of uterine bleeding. Menarche at the age of 12, normal menstruations, no pregnancies, menopause at 50. The patient had received no hormones.

Physical examination: Height 149 cm, weight 76.5 kg. Blood pressure 220/105 mm Hg. Serum bilirubin, alkaline phosphatase, aspartate transaminase (GOT), alanine transaminase (GPT), thymol turbidity test and thrombotest (Owren) were normal. Genital status normal. Vaginal examination revealed slight enlargement of the uterus. Ovarian enlargement was not detected.

An endometrial biopsy specimen showed the histological features corresponding to the proliferative phase of the fertile period. In addition, an endometrial polyp was detected.

The maturation index in the vaginal smear was 0/75/25, which is clearly indicative of increased oestrogen activity.

The methods for determining urinary oestrone, oestradiol and oestriol, total 17-KS, total 17-OHCS and total gonadotrophins and the methods of dexamethasone suppression and ACTH stimulation have been described in previous study (Procopé, 1968). The determination of DHA was performed by Jensen's (1961) method.

Analysis of urine: The excretion of oestrogens (oestrone, oestradiol, oestriol), total 17-ketosteroids (17-KS), dehydroepiandrosterone (DHA) and total 17-hydroxycorticosteroids (17-OHCS) and the results of dexamethasone suppression and ACTH stimulation are shown in Table I. As may be seen in the table, the values for urinary oestrone, oestradiol and oestriol were very high considering the patient's age. The total urinary 17 KS excretion was likewise increased; the proportion of DHA was particularly high. The total urinary 17-OHCS excretion was also elevated. The urinary excretion of total gonadotrophins was low (< 10 MUU).

Adrenal malignancy was suspected, but the patient could not be operated upon owing to severe cardiac insufficiency and poor general condition, and she soon died. At autopsy the following findings were made: In the tracheobronchial lymph nodes there were yellowish metastases, the left pleural cavity contained some 700 ml fluid and the pleura showed metastases. From the peritoneal cavity 2000 ml of purulent fluid was recovered. Yellowish metastases were observed in abundance in the peritoneum, and also in the liver, round the gall bladder and pancreas, and in the sigmoid. At the site of the left adrenal there was a tumour mass weighing 300 g. It was spotted and yellowish, and some capsular tissue was seen in areas, but original adrenal parenchyma was lacking. Histological examination revealed carcinoma of the adrenal cortex (Fig. 1). The metastases showed the same histological structure as the primary tumour. The left kidney was intact and weighed 115 g. The right adrenal was intact but smaller than normal; it weighed 4 g. The right kidney was intact and weighed 105 g. The uterus was large considering the patient's age. The endometrium showed the histological features corresponding to the proliferative phase of the fertile period. The ovaries were small and atrophic: together they weighed only 2 g.

Table I *Urinary excretion of oestrone oestradiol oestriol total 17-ketosteroids (17 KS), dehydroepiandrosterone (DHA) and total 17-hydroxycorticosteroids (17 OHCS)*

No of days	Oestrone (μg/24 h)	Oestradiol (μg/24 h)	Oestriol (μg/24 h)	17 KS (mg/24 h)	DHA (mg/24 h) (per cent)	17-OHCS (mg/24 h)
1	77.5	11 6	25 6	28 0	16.7 (6[illegible]0)	[illegible]3.3
2	63.9	11 8	29.5	7 7	20.1 (73.0)	[illegible]7.5
3	46 6	9.3	21 7	22.2	22.2 (100.0)	39 4
4	42.7	7 4	5 0			
5	71 6	9 4	17.2			
6	49 6	6.8	61[illegible]			
7 (Dexamethasone)						
8 (Dexamethasone)						
9 (Dexamethasone)	63.1	5.5	8 6	31 4	26.5 (84.0)	34 0
10						
11 (ACTH)						
12 (ACTH)	192.0	13 8	32.4	28.6	28.6 (100.0)	31 4

DISCUSSION

Human oestrogen production can be estimated by measuring the urinary oestrogen excretion, by studying the oestrogen effect in vaginal smears and by the histological state of the endometrium Considering the patient's advanced age all these parameters clearly reflected an increased oestrogen production

The excretion of urinary oestrone and oestradio was persistently high, while the excretion o oestriol showed wid fluctuations. This may be ac counted for by disturbances in the conjugation o oestrogens in the liver due to the presence o metastases. The urinary excretion of total 17 KS was also elevated, and the proportion of DHA was very high. In addition, increased values were



Fig 1 Carcinoma of the adrenal cortex (Haemat — van Gieson, 96.)

noted for urinary total 17-OHCS These observations argued in favour of a pathological process in the adrenals.

The urinary excretion of the above-mentioned hormones was not decreased after dexamethasone suppression. This is in agreement with previous findings in carcinoma of the adrenal cortex (Migeon & Gardner 1952 Westman & Luft, 1963). In particular as regards the oestrogens, this observation is significant from the standpoint of differential diagnosis between malignant and be ign adrenal processes. After infusion of ACTH the urinary oestrone excretion showed a clear increase, and a slight increase was noted in oestradiol The urinary excretion of DHA was definitely increased. The absence of a rise in urinary oestriol is obviously due to the fact that the urinary excretion of this component is delayed as compared with that of oestrone and oestradiol (Adlercreutz & Schauman, 1964 Brown et al., 1959 Procopé, 1968), and urine was collected only on the last day f the ACTH infusion and not thereafter In addition, the possibility of disturbances in conjugation due to the presence of liver metastases must be taken into account. An increase in urinary oestrone and oestriol, but not in oestradiol, after ACTH stimulation has previously been reported in cases of carcinoma of the adrenal cortex (West et al., 1958).

Since autopsy revealed atrophic ovaries, it may be assumed that the carcinoma detected in the adrenal cortex was the source of the marked increase in urinary oestrogen excretion and of the obvious oestrogen effect observed in the vaginal smear and the endometrium. This does not, however prove that direct production of oestrogens takes place in an adrenal cortical carcinoma. It is possible that the precursors *of oestrogens*, dehydroepiandrosterone in particular but also androstenedione and testosterone, are converted to oestrogens by peripheral aromatization, as has previously been shown (Braun-Cantilo et al., 196.. Fishman et al 1967 MacDonald et al., 1967 Siiteri & MacDonald, 1963).

The present findings show that the possibility f carcinoma of the adrenal cortex should be considered when signs of an increased oestrogen production are observed after the menopause.

REFERENCES

Adlercreutz, H. & Schauman, K.-O Excretion of oestrone and oestriol in the urine of some male subjects with the Dubin-Johnson syndrome and liver cirrhosis following oral administration of oestradiol benzoate. Acta Med Scand *175* Suppl. *412* 141 1964.

Braun-Cantilo, J. A., La Roche, G., Nevinsky M. & Lawrence, J H. Conversion of testosterone to oestrogens in humans. Acta Isotop (Padova) *1* 351, 196..

Brown, J B., Falconer C. W A. & Strong, J A. Urinary oestrogens of adrenal origin in women ith breast cancer J Endocr *19* 52, 1959

Dczfalusy E. & Luft, R. A qualitative study on the oestrogens excreted by male patient with an adrenal cortical tumour Acta Endocr (Kbh) *9* 327 1952.

Fishman, L. M., Sarfaty G. A Wilson, H. & Lipsett, M. B. The role of the testis in oestrogen production. *I* Endocrinology of the Testis. Ciba Foundation Colloquia on Endocrinology (ed. G. E. W Wolstenholme & M. O'Connor), vol. 16 Churchill, London, 1967

Jensen, C. C. Graviditetsreaktioner och kvantitativa hormonanalyser *I* Kliniska laboratoriemetoder (ed. G Hammarsten), vol. 8, Stockholm, 1961.

MacDonald, P C., Rombaut, R. P & Siiteri, P K. Plasma precursors of estrogen: I. Extent of conversion of plasma Δ-androstenedione to estrone in normal males and non-pregnant normal, castrated and adrenalectomized females. J Clin Endocr 27 1103, 1967

Migeon, C. J & Gardner L. L. Urinary estrogens (measured fluorometrically and biologically) in hyperadrenocorticism: Influence of cortisone, compound F compound B and ACTH. J Clin Endocr *12* 1513, 1952.

Procopé, B. J Studies on the urinary excretion, biological effects and origin of oestrogens in post-menopausal women. Acta Endocr (Kbh) *60* Suppl. *135* 1968.

Siiteri, P K. & MacDonald, P C The utilization of circulating dehydroisoandrosterone sulfate for estrogen synthesis during human pregnancy Steroids 2 713, 1963

Slaunwhite, W R. & Bochvald, K. W Urinary 17-ketosteroids and estrogens in case of feminizing adrenal tumor J Clin Endocr 20 786, 1960.

West, C D Damast, B & Pearson, O H Urinary estrogen excretion in Cushing' syndrome. J Clin Endocr *18* 15 1958

Westman, A & Luft, R Endokrinologi. Stockholm, 1963

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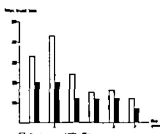
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Acta Obstet Gynec Scand 49 129–131 1970

THE EFFECT OF OXYTOCIN ON THE COMPLICATION RATE OF EARLY THERAPEUTIC ABORTIONS

Elof D. B. Johansson

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Abstract. The complication rate of early therapeutic abortions performed by curettage was studied in four series of patients. In the first series the complication rate was 71%. No or only small dose of oxytocin was given. The second series was performed by one surgeon and 30 I U oxytocin were infused during surgery resulting in only 11% complications. When the oxytocin drip was used by the entire staff the complication rate rose to 18% (third series). This rate was reduced to 12% when the curette was replaced by suction device (fourth series). Oxytocin in high enough dosage to cause contraction of the myometrium in early pregnancy drastically reduced the amount of bleeding during curettage. The number of infections was also reduced.

In the past, most therapeutic abortions in Sweden have been performed during the 12th–20th week of gestation. At the Department of Obstetrics and Gynaecology in Uppsala, the number of abortions carried out before the 12th week of pregnancy has increased sharply in the last few years, due to the speed up in the bureaucratic procedures and the rising awareness of the advantages of an early operation (Table I). Except for 1964 when vaginal hysterotomy was used as often as curettage, cervical dilation and curettage have been the major technique.

During 1965 an increasing number of abortions were performed before the 12th week. Due to the many complications, especially haemorrhage and infection, the present study was started in an effort to lower the complication rate. As blood loss was the main problem, a large dose of oxytocin (30 I U) was administered during the operation.

MATERIAL AND METHODS

Series 1 included all therapeutic abortions during 1965 at the University Hospital that were performed by curettage. The patients were given 1 ml Methergin (Sandoz) at the end of the operation.

Series 2 was an experimental series studied by the author in 1966. All patients before the 13th week of gestation admitted to the clinic from January to May were treated by the following method:

Narcosis. Intravenous penthotal and oxygen-nitrous oxide mixture were administered.

Cervical dilatation was performed to the number of Hegar dilator corresponding to the week of gestation.

Oxytocin drip 30 I.U. Syntocinon (Sandoz) in 500 ml 5.5% glucose solution was infused throughout the operation, starting when the dilatation had reached Hegar number 8. The drip was allowed to run at maximum speed at first i.e., about 15 ml per minute (about 1 I U per minute).

Curettage. The largest blunt curette possible was used. On many occasions the conceptus presented itself at the external os even before the curettage was started. The blood loss during the operation was measured. Pulse and blood pressure were also recorded.

Series 3. The same method as in series 2 but used by the entire staff of the hospital during 1966–1967.

Series 4. The same method as in series 2 with the exception that the curette was replaced by suction device (Melin, 1964, Vladov et al. 1965, Perez et al., 1965).

DEFINITIONS

Bleeding during surgery. A blood loss of 500 ml or more was considered as a complication. The conceptus and the liquor amnii were included in this figure. A fall in the haemoglobin concentration of 10% or more was also recorded as complication.

Bleeding after surgery. All excessive bleeding occurring within 7 days of the operation was recorded as complication.

Salpingitis. Three of the following symptoms had to be present. Fever, bilateral pain and tenderness in the lower abdomen, pain in the adnexa on bimanual palpation, adnexal swelling or rise in the blood sedimentation rate.

Temperature rise of more than 38°C on more than one occasion postoperatively was recorded as complication.

Table I *Total number of therapeutic abortions at Akademiska Sjukhuset Uppsala (UAS), 1964–1967 and the number of these abortions performed by curettage*

The 1967 figure includes suction curettage

Year	Total number of therapeutic ab at UAS ( )	By curettage ( )	Percentage curettage of total abortions
1964	185	6	3.2
1965	298	29	9 7
1966	279	76	27
1967	425	170	40

Number of days in the hospital The day of surgery was counted as day number one The day of leaving was included.

Other complications during surgery In this group were included trauma to the cervix or vagina that required attention, perforation of the uterus and failure to remove the conceptus.

RESULTS

The number of patients in the four groups with their mean duration of pregnancy in weeks, length of hospital stay and the percentage of patients with complications are shown in Table II In Table III the different complications are reported. Some patients had more than one complication.

During 1965 the complication rate was about 70% Out of 11 patients with bleeding during surgery 6 bled more than 1000 ml and 8 developed salpingitis. The complication rate was drastically reduced during the experimental second series, when a large dose of oxytocin was infused. Only 3 patients had a temperature rise and only one developed endometritis.

In the third series, in which the method of the second series was used by the entire staff, the complication rate rose from 11 to 18 . When the suction curettage was introduced (series 4), the complication rate again went down to 12' There was no massive haemorrhage during curettage in series 3 Five patients bled during the evacuation of the uterus but three of them bled just about 500 ml and none bled mor than 1000 ml Only one patient of the five developed salpingitis.

In the first and second series there were no other complications during surgery In the third series there were four perforations of the uterus, one cervical rupture and two lacerations of the cervix, total 7 patients. In the fourth series there was one perforation of the uterus, one cervical rupture and 2 cases where the conceptus was left behind All the patients with these complications appeared well at the follow-up examination –3 weeks after the abortion However at the present time the possibilities of late sequelae cannot be excluded.

No significant drop in blood pressure was noted.

Table II *Complications hospital stay length of pregnancy and number of patients in the four series of therapeutic abortions*

S D – Standard deviation

Series	Period	N of patients	Mean duration of pregnancy (weeks) (±S.D)	Hospital stay in day (±S.D)	Percentage complications
1	1965	29	10±1	6±3 8	71
2	1966	27	12±1.6	4±1.3	11
3	1966–1967	84	11±1 6	4±3 4	18
4	1967	133	11±1.5	4±3 8	1

Table III *The number (n) of different complications in each of the four series of therapeutic abortions*

Series	P tients ( )	Bleeding during surgery ( )	Other complications during surgery ( )	Bleedi g after surgery ( )	Salpingitis ( )	Temperature rise ( )
1	29	11	0	9	11	3
2	27	0	0	0	0	3
3	84	5	7	5	4	1
4	133	0	4	7	4	8

On awakening the patients often noted that their preoperative hunger and thirst were gone, probably as a result of the 500 ml 5.5% glucose infusion.

DISCUSSION

The pregnant uterus around the 12th week of gestation is rather insensitive to oxytocin. Caldeyro-Barcia (1961) has shown that 0.128 mU oxytocin per minute for 2 hours (total 15.36 I.U.) produces strong contraction in an uterus of 12th week gestation. As most of the abortions were carried out before the 12th week, the dose of oxytocin was fixed at 30 I.U. Fortunately oxytocin is well tolerated. Bieniarz (1961) has infused 16 I.U. oxytocin per minute, the only side effect being a moderate and short drop in the blood pressure. The infusion rate in this work was never above 1.5 I.U. per minute. No significant drop in blood pressure was noted.

Oxytocin rarely gives rhythmic contractions in 12th week pregnant uterus but rather a prolonged contraction (Smyth, 1961). In most cases the cervix is relaxed but in some patients the cervix will contract also, according to Smyth (1961). To avoid this effect, the oxytocin infusion was only started when most of the cervical dilation had been done. No cervical contraction was observed in this study. To avoid a reduction of contractability of the uterus, halothane ("Fluothane") should not be used to anaesthetize these patients, as halothane relaxes the myometrium and reduces its irritability (Vasicka & Kretchmer 1961. Crawford, 1962).

Guttmacher (1964) recommended the use of 20 I.U. Syntocin to reduce the risk of uterine perforation and to diminish bleeding. No data of the reduction of these complications was given. Klimek & Kordecki (1963) compared the effect of oxytocin on the bleeding during the curettage with 138 patients who got no oxytocin. However 34 of these 138 patients bled so much that oxytocin had to be given, making statistical analysis impossible.

I review of the complication rate of therapeutic abortions at the Toronto General Hospital during 1 years, Sprvak (1967) reports an overall complication rate of 19.3%. However he only includes major complications. Using his criteria there would be no bleeding complications in our series 3 and 4 as he allowed a blood loss of up to 1000 ml.

In the first series, bleeding during the curettage was clearly linked with salpingitis. In cases with low blood loss, the number of infections were reduced. As salpingitis is a severe complication, which in some patients gives tubal occlusion and sterility the reduction in this complication is very important.

As seen in Table II the patients in series 2 were at a somewhat later stage of gestation. Three patients were in the 15th week but could still be treated by curettage without difficulties. Due to the contraction of the uterus, the volume of the uterine cavity was reduced and the foetus could easily be grasped by the forceps and pulled out. The cervix had been dilated to Hegar number 15. It is possible that the oxytocin infusion facilitates safe therapeutic abortions by curettage up to the 14th week. However the present series are too small to validate such a conclusion.

The three series with oxytocin infusion had a very much lower incidence of complications than the 1965 series. The severity of the complications was also reduced. With fewer complications the stay in hospital could be reduced (Table II), freeing much needed hospital beds.

REFERENCES

Bieniarz J. Oxytocin (ed. R. Caldeyro-Barcia & H. Heller), p. 80. Pergamon Press, 1961

Caldeyro-Barcia, R. & Sereno, J. A.: *I* Oxytocin (ed. R. Caldeyro-Barcia & H. Heller), p. 177. Pergamon Press, 1961

Crawford, J. S. Brit J Anaesth *34* 386 1962.

Guttmacher A. F. Clin Obstet Gynec *7* 100 1964.

Klimek, R. & Kordecki, Z., Ginek Pol *34* 491, 1963

Melin, E. J. Akush Ginek *6* 133 1964.

Peretz, A. Grunstein, S. & Brandes, J. M. Harefuah *69* 365 1965

Smyth, C. N. *In* Oxytocin (ed. R. Caldeyro-Barcia & H. Heller), p. 281. Pergamon Press, 1961

Spivak, M. M. Amer J Obstet Gynec *97* 316, 1967

Vasicka, A. & Kretchmer H. Amer J Obstet Gynec *82* 600, 1961

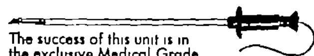
Vladov E., Ivanov I. Angelov A. & Rakilovska, L: Gynaecologia *159* 54, 1965

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OXYPHENBUTAZONE IN VAGINAL OPERATIONS FOR GENITAL PROLAPSE

A Double-blind Study

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Abstract. The effects of oxyphenbutazone (Tanderil) during the first week following vaginal operations for prolapse have been studied by the double-blind technique. The series comprised 84 patients, 41 of whom received the drug and 43 the placebo. A loading dose was given on the day before the operation, and the medications continued until the seventh post-operative day. There was a statistically significant decrease in the use of analgesics, and a persistent but not significant lowering of the rectal temperature in the oxyphenbutazone group. The recovery of bladder function was equal in the two groups, as were the side effects and complications. Judged by the nurses' unbiased report of the post-operative course, there was a tendency towards an uncomplicated course in the oxyphenbutazone-treated as compared with the placebo-treated patients.

Oxyphenbutazone (Tanderil) is a drug with many actions, which has mainly been used in rheumatic disorders. It has antipyretic, analgesic and anti-inflammatory properties (Goodman & Gilman, 1965), from which we may also anticipate beneficial effects in various surgical conditions. This has been substantiated in a number of experimental and clinical studies. Oxyphenbutazone medication has resulted in fewer fever reactions (Billow et al. 1962, Heimann & Olsson, 1962, Haeger & Borg, 1965), less post-operative pain (Radman et al. 1961, Fraser et al., 1961, Jordheim & Knoff, 1968), less post partum pain (Steenstrup, 1965, Wisborg, 1966), and a reduction of redness, swelling and oedema, both following operations (Fraser et al., 1961, Radman et al. 1961, Wisborg, 1966), following fractures (Gruber 1965, Lechner 1965) and in inflammatory conditions of varying aetiology (Scholl, 1961, Heimann & Olsson, 1962, Billow et al., 1962, Haeger, 1963).

When the present study was undertaken, no investigation had satisfactorily answered the question of the possible advantages of oxyphenbutazone in one particular type of gynaecological operation. This, therefore, is a planned, prospective double-blind study which primarily intended to find out whether the patients would experience less discomfort in the immediate post-operative period following vaginal operations for prolapse, if oxyphenbutazone were given. Recently Jordheim & Knoff (1968) have published the results of an essentially similar study which compares the results for two groups of patients operated on during two different time periods. Their results seemed to indicate an antipyretic and an analgesic effect in the oxyphenbutazone-treated group.

MATERIAL

Patients admitted to the hospital, in whom a vaginal operation for genital prolapse or isolated stress incontinence was planned, were included in the study. However, since oxyphenbutazone is reported to be toxic, and may cause sodium retention and untoward effects from various organs, such as the liver, the stomach and the bone marrow, patients belonging to the following categories were excluded: (*a*) age over 75 years, (*b*) heart failure, (*c*) severe hypertension, (*d*) gastric or duodenal ulcer, (*e*) allergy, (*f*) liver disease, and (*g*) anaemia below 11 g haemoglobin per 100 ml.

The series was to include 100 patients, each of whom was allotted a numbered bottle. However, in a number of cases the operation was postponed, or conservative treatment decided upon, following the start of drug medi-

the amounts of analgesics given; secondly oedema, by the ability to urinate; and thirdly inflammatory reactions, by the rectal temperature and by wound healing. Evidently some of these reactions may result from an interaction between two or three factors, but that does not affect the analyses, however.

When there was an obvious homogeneous distribution between the two treatment groups no statistical analysis was performed. For comparisons between two approximately normal distributions Student' *t*-test was used, and for other comparisons the χ-test or two-by-two (four-fold) table test was used.

RESULTS

The results are shown in Tables IV to X inclusive.

Table IV shows the distribution of analgesic injections and tablets for the two groups, excluding patients who had one of the less extensive operations. The table gives the impression that the patients in the placebo group (*b*) tended to receive more analgesics than those in the oxyphenbutazone group ( ). This was verified by the analysis of each component separately which was significant both for injections (0.05 > *P* > 0.025), and for tablets (*P* = 0.01).

The next T bles (V and VI) show the bladder function, expressed as the number of days before spontaneous micturition occurred (Table V) and the number of days when residual urine was over 50 ml. Neither of these two parameters gave any evidence of difference between the two groups. Our department normally uses an indwelling catheter for 5 days in these cases, and we were interested to see how quickly bladder function was restored to normal in many of the patients in this trial.

T ble VII shows the patients' temperature post-operatively expressed as the mean of the morning

Table IV *Post-operative medication of analgesics, including all the patients who had anterior and posterior colporrhaphies including amputation of the cervix*

(*a*) *Oxyphenbutazone (30 patients)*

		Number of injections of morphine (or equivalents)				
		0–1	2 3	4–5	6<	Total
No of analgesic tablets	0	4	8	1	0	13
	1 2	0	6	1	2	9
	3–4	1	1	1	0	3
	5<	0	3	1	1	5
	Total	5	18	4	3	30

(*b*) *Placebo (32 patients)*

		Injections (see (*a*))				
		0–1	2 3	4–5	6<	Total
Tablets (see (*a*))	0	0	5	2	1	8
	1 2	1	3	3	1	8
	3–4	0	4	2	0	6
	5	1	6	2	1	10
	Total	2	18	9	3	32

Statistical evaluation	Oxyphenbutazone	Placebo	Student' *t*-test
No of morphine injections (mean S E mean)	2.90 ·0.34	3.72 + 0.16	0.05 *P* 0.025

(Calculations based on additional information to that in Table) The use of analgesic tablets was compared in two-by-two table, with the dividing line drawn between 2 and 3 tablets. This gave probability (*P*) of true difference of 0.01

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Table V *Post-operative bladder function. Period before spontaneous micturition*

The table includes all the patients who had anterior colporrhaphies. $\chi^2 = 2.03$ d.f. = 3 *P* = 0.5

	Oxyphenbutazone		Placebo	
No. of days	No. of patients	%	No. of patients	%
0	12	32	17	42
1	10	28	12	29
2 or 3	9	24	5	12
4+	7	18	7	17
Total	38	100	41	100

Table VI. *Post-operative bladder function. Period of residual bladder urine of 50 ml or more*

The table includes all the patients who had anterior colporrhaphies. Obviously no difference between the groups

	Oxyphenbutazone		Placebo	
Maximum no. of days	No. of patients	%	No. of patients	%
0 or 1	9	24	7	17
2 or 3	9	24	11	27
4 or 5	8	21	9	22
6 or 7	5	13	6	15
8+	7	18	8	19
Total	38	100	41	100

Table I *Age distribution*

	No of patients	
	Oxyphenbutazone	Placebo
35–39	3	1
40–49	10	11
50–59	14	14
60–69	12	16
70–74	2	1
Total	41	43

Table II. *Clinical conditions*

	No of patients	
	Oxyphen-butazone	Placebo
Cystocele	30	33
Rectocele	23	2[illegible]
Enterocele	1	5
No uterine prolapse	8	12
Subtotal prolapse	23	21
Total uterine prolapse	10	10
Stress incontinence	10	13
Previous vaginal operation	3	1

cation. After exclusion f these patients the series comprised 84 patients, of whom 41 received oxyphenbutazone and 43 the placebo. The age distribution of the patients and their indications for operation are shown in Tables I and II It is seen that the two groups are very comparable in these respects.

METHODS

Th drug medication

Oxyphenbutazone and the placebo were provided in numbered bottles, each containing .8 tablets of similar shape and co our Each oxyphenbutazone tablet contained 100 mg f the drug. The dosage scheme was as follows.

The day before operation,	4 tablets
Second and third post-operati days,	tablets 3 times daily
Fourth to seventh post-operative days,	1 tablet 3 times daily

None of the patients had to discontinue the medication because of untoward reactions which might be due to the drug.

The code was broken at the end f the investigation.

The operation

I the majority of cases the operation consisted of anterior and posterior colporrhaphy combined with an amputation of the cervix. In a few cases the cervix was l intact. A few cases of only anterior or only posterior c porrhaphy were also included. Table III shows the c ferent types of operation, which are seen to be simila distributed in the two treatment groups. The operatı were performed by nine different doctors, each of he had an almost equal share of oxyphenbutazone and pla bo treated patients.

The post-operative course

Analgesics were given as required. During the first c or two days morphine-like analgesics wer given as i jections, later phenacetin and salicylate containing table were given.

The previous department routine of giving sulphonamid to prevent urinary infections was unfortunately not d continued, as planned, when the trial was started, so th a meaningful comparison f post operative infections worthless.

Prophylactic anticoagulants were not given routinel nor were they ever required for therapy

The patients did not have indwelling catheters. The were catheterized two or three times daily if attempt to urinate spontaneously failed. Residual bladder urı was measured daily until the volume was less than 50 ml

The rectal temperature was measured each morning an afternoon.

A leucocyte count was performed, and the transam nases, SGOT and SGPT were measured on the sixth post operative day

I uncomplicated cases, which includes the ast majori ty the patients left the hospital on the ninth post-opera th day

F completeness it should be mentioned that all pa tients over 50 years of age received an injection of 10 mg oestradiol valerat in oil preoperatively

Statistical evaluation

The aim was to study separately the three factors with which oxyphenbutazone might interfere. Firstly pain, by

Table III *Operation*

	No of patients	
	Oxyphen-butazone	Placebo
Anterior nd posterior colporrhaphy with amputation of the cerv	30	3
Anterior and posterior colporrhaphy	4	6
Anterior colporrhaphy th or without mputation (resection) of the cervix	4	3
Posterior colporrhaphy with or without amputation (resect on) of the cervix	3	2
Total	41	43

therefore falling in the group severe nursing problems

DISCUSSION

In accordance with earlier investigations, the present study revealed certain post operative effects which must be, or which are most likely to be, due to oxyphenbutazone. I particular the results are in perfect agreement with those of Jordheim & Knoff (1968), who also found fewer fever reactions and a reduction in the use of analgesics.

The significant reduction of analgesic medication was not unexpected, since the analgesic action of oxyphenbutazone has been clearly established (Goodman & Gilman, 1965).

The analysis did not definitely establish an antipyretic action of the drug, but there was a persistent trend towards a low·r temperatur in the oxyphenbutazone group In the light of what is known about an antipyretic effect of the drug (Goodman & Gilman, 1965), onetailed Student's t-test may be regarded as permissible, making the difference of Period III in Table VII significant at the 5% level. A significant difference at this late stage of the post operative course agrees well with the time course of the effects of the drug, to be mentioned below

The anti-inflammatory effect of oxyphenbutazone could not be detected by evaluating bladder function, nor by delayed wound healing. It was thought that post-operative oedema might be an important factor in the re-establishment of bladder function This may have been misjudgement, however pain and other nerve reactions probably being more important (Greenhill 1963)

Oxyphenbutazone has been shown to encourage healing, judged by the tensile strength f experimental wounds in rabbits (Brunlov & Zederfeldt, 1965) In the present investigation, no obvious difference could be found as delayed healing occurred equally in the two groups (T ble IX), but unfortunately a more discriminating method f evaluating the wounds was not used.

Based on this investigation nothing can be said about the anti-inflammatory action of oxyphenbutazone except that this may be contributing factor in the analgesic and in the temperature lowering ffects Anti-inflammatory in this connection should not be confused with anti-biotic, in fact, oxyphenbutazone has been shown to suppress the symptoms and signs of severe bacterial infection (Fraser et al 1961).

An important point concerning the use of oxyphenbutazone is that the drug exhibits its maximum effect only after a loading dose and 3 days of therapy (Fraser et al., 1961). This means that an optimum post-operative effect can only be obtained if the medication starts 3 days pre-operatively which is impractical in most cases. In the present investigation the loading dose was given on the day before the operation.

The practical problem still remains a question for individual judgement. Does oxyphenbutazone reduce the post-operative discomfort of these patients to such a degree that it may be recommended for general use? The relief of pain, and the lowering f the temperature can easily be achieved by other means if this symptomatic relief is the only advantage. If on the other hand, the drug promotes the general well-being of the patient by a more profound action on the healing process, then its use may be justified Judged by the nurses unbiased evaluation of the post-operative course (Table X), the latter notion does have some support. Unwanted drug reactions give rise to no problems during such a short course of therapy if the patients are selected carefully but the necessity f a loading dose and a delay of 3 days before the full effect is reached is an obvious disadvantage.

The decision to use oxyphenbutazone in vaginal operations must be a matter for individual judgement Routine use for all patients is hardly justified, but its selective use with due consideration to the spectrum of contra-indications, which has only been touched on briefly here is likely to benefit the patients.

ACKNOWLEDGEMENT

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REFERENCES

Bellew B W Paley S, 6 Carey R. M., Lowen, H., Mihaly J M Thompson, E. A & Ross, C., J New Drugs 2 115 196_
Brunlov, U & Zederfeldt, B., I Die Postoperative Entzündung und ihre Behandlung (ed. U F Gruber & E Wilhelmi), p 39 Davos 1964. Karger Basel and New York, 1965

Table VII *Post-operative temperature*[a]

Calculations for Student's t-test were based on more decimals than those given in the Table

Period	Day (0 = day of operation)	Oxyphenbutazone (41 patients)		Placebo (43 patients)		Student's t-test
		Temp.	S.E.	Temp	S.E.	
I	0, 1, 2	37.42	0.03	37.45	0.02	$0.5 > P > 0.4$
II	3, 4, 5	37.23	0.03	37.29	0.03	$0.3 > P > 0.2$
III	6, 7, 8	37.17	0.03	37.25	0.03	$0.1 > P > 0.05$

[a] Measured as average of morning and afternoon rectal temperatures (centigrade) in successive 3-day periods.

Table VIII *Laboratory values on the sixth post operative day*

The numbers of patients in the groups range from 33 to 39. None of the differences were statistically significant by the Student's t-test

	Oxyphenbutazone		Placebo	
	Mean	S.E.	Mean	S.E.
Leucocytes/mm^3	7900	300	7400	270
SGOT	18.3	1.6	21.4	1.6
SGPT	28.0	2.4	34.3	3.2

Table IX. *Complications*

	No. of patients	
	Oxyphen-butazone	Placebo
Nausea after operation day	3	8
Vomiting after operation day	5	
Allergic reactions	0	2
Phlebitis or emboli	0	0
Delayed wound healing		

Table X. *Post-operative problems, as evaluated by the ward nurses*

	Oxyphen-butazone	Placebo
No complications	7	3
Some nursing problems	31	33
Severe nursing problems	3	7
Total	41	43

and afternoon temperatures in successive three-day periods. This implies that in each patient the mean for each period is the average of six single measurements. It is seen that for each period the mean temperature was lower in the oxyphenbutazone group than in the placebo group, but the differences are not statistically significant. The persistent trend from period to period is suggestive, however. Therefore the temperature readings were also compared by counting the patients who had an average below 37.3° during the first three-day period, which was 16 in the oxyphenbutazone group and 9 in the placebo group. This difference was almost significant in a two-by-two table test ($P = 0.06$). The same trend was found by counting the patients who had temperatures above 38.0°, 38.5° and 39.0° in the two groups, but significant differences were not found.

The leucocyte counts and the transaminase values on the sixth post-operative day were almost identical in the two groups, using the means and standard errors as a basis for comparisons (Table VIII). Remembering that oxyphenbutazone might have an adverse effect on only a few susceptible patients, it should be mentioned that SGOT values over 50 units were found in – oxyphenbutazone treated patients against 5 placebo treated patients. SGPT did not reach pathological levels, nor did the leucocyte count go below 4000 per mm^3 in any of the groups.

Complications were also evenly distributed, as seen in Table IX. Finally, the ward nurses' evaluation of the post operative course is shown in Table X. The vast majority of patients fell not unexpectedly in the group labelled "some nursing problems", meaning that they experienced a certain degree of discomfort. Taking the two extremes, oxyphenbutazone treated patients more often had an uncomplicated course while the reverse was true of the placebo treated patients, who more often experienced severe discomfort.

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LOCALIZATION OF A MISSING IUD WITH THE HELP OF PLAIN X RAY EXAMINATION AND A SECOND IUD

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Abstract. In cases where it is uncertain whether an inserted IUD has been expelled without the patient's knowledge, has perforated the uterine wall, or is still in its proper intrauterine position, plain X-ray examination performed after insertion of a second IUD usually clarifies the situation. This technique is very simple from both the gynaecologist's and the roentgenologist's point of view.

Every worker in the field of fertility control is likely to be faced sometimes with the situation when the tail of an intrauterine contraceptive device (IUD) cannot be detected on gynaecological examination. The question then to be answered is whether the IUD has been expelled without the patient's knowledge, is still in its proper intrauterine position, or has been displaced outside the uterus. If an IUD without a cervical appendage is used, this uncertainty is of course the rule, but the problem may arise also with tailed IUD's. Tietze (1965) reported translocation of the Birnberg bow in 0.2% of cases, while Ratnam & Yin observed a much higher frequency of translocation of Lippes loop after insertion in the post partum period (1968). Quite recently Tacchi (1968) reported that the SAF T-coil, in spite of its name, may perforate the uterus. However, if the tail of the IUD cannot be palpated or seen, there is no definite proof of expulsion or translocation to the peritoneal cavity. The tail is not infrequently drawn up into the cervix or uterine cavity without the device being displaced (Rosen, 1965; Ratnam & Yin, 1968). The tail of the Margulies spiral too may occasionally be retracted so high up as not to be detected (Tötterman, 1966).

Since IUD's are radioopaque, an X-ray examination is helpful in localizing the device. Unfortunately only gross translocations can always be demonstrated by simple radiography. In the case of para-uterine translocation a hysterogram may be needed to obtain full proof (Fuchs et al., 1965; Ratnam & Yin, 1968). By this technique it ought to be possible to detect even partial translocation of an IUD (cf. Tacchi's case 1, 1968; Unnérus, 1968). IUD's in intrauterine position may also be localized by an echo technique using the Beolocator (Jorgensen, 1964; Fuchs et al., 1965). With this method a partial translocation may however escape attention.

Fuchs et al. (1964) considered hysterography to be too complicated a procedure for routine use in the search for lost IUD's. Since we are of the same opinion, we have proceeded as follows: If an IUD is not detected in spite of forceps exploration of the endocervix, and if exploration of the uterine cavity sometimes performed with a Birnberg hook also proves unsuccessful, a new IUD has been immediately inserted. We have preferred to use a small Margulies spiral for this purpose. Then the patient has been sent for plain X-ray examination. First, a lateral view of the true pelvis is taken. Provided that the IUD can be identified on this, an anteroposterior (*a–p*) view is taken of the same region. If no IUD is seen on the lateral view, an antero-posterior view of the whole abdomen is taken instead. As a rule the X-ray examination is not urgent, and may be postponed till a time that suits the patient and the X-ray department. If the films show two IUD's lying close to and covering each other, it can reasonably be assumed that both lie within the uterine cavity. The Margulies spiral, which was later inserted, is then readily extracted. Even

Fraser W D Beardall, P J & Maughan, G B., Canad Med Ass J *85* 295 1961
Goodman, L. S. & Gilman, A. The Pharmacological Basis of Therapeutics, 3rd edn. Macmillan, London, New York and Toronto, 1965
Greenhill, J P Surgical Gynecology 3rd edn. Year Book Medical Publishers, Inc., Chicago, 1963
Gruber U F., *I* Die posttraumatische Entzündung und ihre Behandlung (ed. U F Gruber & E. Wilhelmi), p. 76. Davos 1964 Karger Basel and New York, 1965
Heimann, P & Olsson, O. Sv Läkartidn *59* 2673 1962.
Haeger K., Sv Läkartidn *60* 1474 1963
Haeger K. & Borg, L. Med Welt *33* 1861 1965
Jordheim, O & Knoff, T., T Norske Laegeforen *88* 2020, 1968
Lechner G *In* Die posttraumatische Entzündung und ihre Behandlung (ed. U F Gruber & E. Wilhelmi), p 94 Davos 1964. Karger Basel and New York, 1965
Radman, H. M., Campbell, C. & Coplan, R. S., Amer J Obstet Gynec *81* 344 1961
Scholl, O Med Klin *56* 1055 1961
Steenstrup O R., Nord Med *74* 1050 1965
Wisborg, T., Nord Med *75* 444, 1966.

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Fig. 3 Lateral view of the same case as in Fig. 2, showing that the two IUD' are situated close on each other The two views together allowed the conclusion to be drawn that both IUD' were properly located in the uterus.

REFERENCES

Fuchs, F F Bachman, M. I & Nakamoto, M Amer J Obstet Gynec 93 128, 1965

Jorgensen, T E Nord Med 82 1143 1964

Kaitunen, S S & Ylä, J C. K., Brit Med J 1 612, 1968.

Rosen, E Amer J Obstet Gynec 93 896, 1965

Tacchi, D J Obstet Gynaec Brit Comm 75 1176, 1968.

Tietze, C Sixth Progress Report, Part 1 National Committee on Maternal Health, New York, 1965

Totterman, L. E Acta Obstet Gynec Scand 49 57 1970

Unnérus, C.-E Personal communication 1968

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Fig. 1. A case in hlch it was assumed that tw Margulies spirals had been expelled, one after the other, without the patient's knowledge. A Birnberg bow was then easily inserted and an X-ray examination was per formed a couple of months later. This *a-p* view shows the three devices. The uterus was large and the cervix e ongated.

If both IUDs are unintentionally removed, this can hardly be considered a complication.

As may b seen in Figs. 1–3 the second IUD aided proper localisation of the first one, and the conclusion could b drawn that there had been no displacement. In suspect cases additional exposures from suitable angles can b made or hysterography can be performed. In a case like Tacchi's case 1 a second IUD would probably have sufficed to show that the SAF-T-coil was not in its prop r intrauterine position. However a case of slight partial translocation through the wall of the uterine fundus (Unnérus, 1968) seems likely to escap detection. Nevertheless, since such cases obviously are rare they do not seem to provid an argument against using the simple second IUD technique described above in the search for a missing device, if hysterography is considered not to be primarily indicated.



Fig. *A p* iew taken in a case in hich Lippe loop w lost. The small Margulies spiral seen on the X-ray at the same level the loop inserted w thout any dif ficult and it likewise readil emoved about week after the X-ray exam ination, while the Lippe loop remained in position. The loop as remo ed one y ar later w th the aid f B rnberg hook.



Fig. 3. Lateral view of the same case as in Fig. 2, showing that the two IUD's are situated close on each other. The two views together allowed the conclusion to be drawn that both IUD were properly located in the uterus.

REFERENCES

Fuchs, F. F., Buchman, M. I. & Nakamoto, M. Amer J Obstet Gynec 93 128, 1965.

Jorgensen, T. E. Nord Med 82 1148, 1964.

Raman, S. S. & Yim, J. C. K. Brit Med J 1 612, 1968.

Rosen, E. Amer J Obstet Gynec 93 896, 1965.

Tacchi, D. J Obstet Gynaec Brit Comm 75 1176, 1968.

Tietze, C. Sixth Progress Report, Part I. National Committee on Maternal Health, New York, 1965.

Tötterman, L. E. Acta Obstet Gynec Scand 49 57 1970.

Unnérus, C. E. Personal communication 1968.

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SERUM CONCENTRATION OF HUMAN PLACENTAL LACTOGENIC HORMONE (HPL) IN PREGNANCY COMPLICATIONS

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Abstract HPL concentration was determined by an immunochemical method from 48 serum samples of 41 women ith complications of pregnancy While no correlation was found between HPL and pregnancy eek, statistically significant correlation was observed between HPL and oestriol. Placental and infant birth weights had highly significant correlation ith HPL. No significant deviation from the standard was observed in the serum HPL of toxaemia patients, or in HPL of those ith prolonged pregnancies or variations in foetal heart rate. Because of great individual variation no general limits could be calculated for maternal serum HPL concentration at 30–42 eeks of pregnancy

The concentration of human placental lactogenic hormone (HPL) in the serum of a normal pregnant woman rises throughout pregnancy and reaches its highest level at the time of birth. After removal of the placenta HPL disappears from maternal blood within a few hours (Beck et al., 1965). At term the level of HPL is related neither to placental weight nor to the infant's birth weight. The blood content of HPL does not change with the time of day the activity of the subject or the blood glucose level (Spellacy et al., 1966) It has been established that HPL is produced by the trophoblast. By immunofluorescent studies HPL has been localized in the syncytio-trophoblast (Sciarra et al 1963).

In search for indicators of placental function we compared the serum HPL levels measured immunochemically with urinary oestriol excretion, placental and infant birth weights, and duration of gestation at different stages of pathological pregnancies

MATERIAL AND METHODS

Specif anti-HPL serum, prepared in rabbit by immunizing it ith purified HPL preparation (Tallberg et al., 1965), was used. The immunochemical measurement of HPL was performed by the radial immunodiffusion technique of Mancini et al. (1965). A mean HPL level of 20 sera from normal healthy pregnant women at term served as standard and was designated by the number 100. The HPL content of the sera examined was expressed according to this level, as percentage of the standard. Oestriol was determined by modified method of Brown (1960) Serum and urine samples for HPL and oestriol determinations were collected over the same two day period in each case.

Forty-eight serum and urinary specimens from 41 pregnant women were examined. All these ere patients who required admission to hospital because of pregnancy complications such as variation in foetal heart rate (15 cases), toxaemia (13), or postmaturity (7), diabetes mellitus (2), anaemia (1), thyrotoxicosis (1), placenta praevia (1) and jaundice of pregnancy (1). Correlation analyses were performed between HPL and oestriol, HPL and placental weight, HPL and infant birth weight, and HPL and duration of gestation.

RESULTS

The overall results are presented in Table I, and the results of the correlation analyses in Table II. The mean HPL value in the series was *103 8*, which is quite close to the standard. In the three major complication groups the following mean values for HPL were obtained. variation in foetal heart rate 113.2, toxaemia 98.6 and postmaturity 93.0 None of these represent a significant difference from the standard.

On the basis of 30 specimens from 23 patients HPL and daily output or urinary concentration of oestriol showed a correlation ($r = 0.40 \pm 0.17$ and 0.46 ± 0.17 respectively (Figs. 1 and 2), which is statistically significant $t_{0.975} = 2.05 < t = 2.3$ and $t_{0.99} = _.47 < t = 2.9$ respectively). At the time of birth maternal serum HPL concentration was re

Table II *Correlation coefficients (r) and the respec tive standard errors (ε) of maternal serum HPL concentration and urinary oestriol excretion, infant and placental eights, and duration f gestation*

number of variable pairs

Oestriol (mg/24 h)	Oestriol (mg/ml)	Infant weight	Placental weight	Pregnancy week
0 40	0 46	0 54	0 64	0,14
0 17	0,17	0 14	0,13	0,15
30	30	34	34	46

concentrations (below 80% from the standard) the lowest Apgar score of the child was 9

DISCUSSION

The radial immunodiffusion method is a simple and reliable technique for the measurement of serum proteins provided that a specific antiserum is available. For clinical use the weakness of the method is that the results cannot be recorded for 48 hours Our results agree in general with previous observations (Spellacy et al., 1966), but we observed a highly significant correlation between HPL and placental weight. That no correlation between HPL and pregnancy week was found is considered to be due to the nature of the pregnancy complications, where continuing placental and foetal development remained questionable. Moreover our findings reflect marked individual variations in serum HPL concentrations between different individuals. The fairly poor correlation between HPL and oestriol may be because of different sources of origin of these hormones. While HPL is a placental product, oestriol excretion depends on the function of the foetoplacental unit. However for clinical use, the results indicate that no definite conclusions about placental function or f etal state are justified on the basis of single HPL determinations from maternal serum. It is possible that marked reduction in maternal HPL concentration might indicate danger to the foetus, but this remains to be established. Large series are necessary to find out the significance of HPL in different pathological conditions of pregnancy

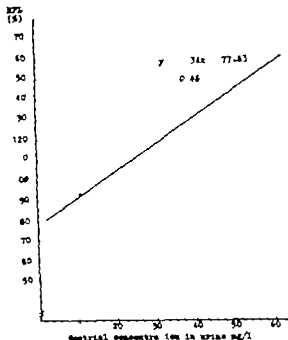


Fig 2 Comparison of serum HPL and urinary oestriol concentration.

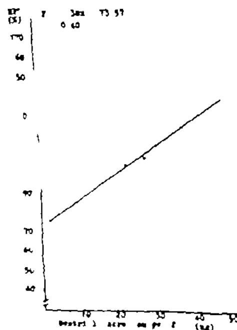


Fig 1 Comparison of serum HPL and urinary oestriol excretion per h

Table I *Maternal serum HPL, urinary oestriol excretion, infant and placental weights and duration of gestation in 41 complicated pregnancies*

T = toxaemia, D = diabetes, A = anaemia, Thyr = thyrotoxicosis, HR = variation in foetal heart rate J = Jaundice of pregnancy PP = placenta praevia, Prol = duration of pregnancy more than 41 weeks

No	*HPL* ([illegible])	*Oestriol* (mg/24 h)	*Oestriol* (mg/l)	*Infant's* weight (g)	*Placental* weight (g)	*Duration of* gestation (weeks)	Complication of pregnancy
1	154	14	23	3870	770	39	T
	107	16	12	—	—	34	T
	110	16	11	2400	540	37	
3	138	41	26	3450	720	37	D
4	46	22	12	—	—	37	T
4	36	13	7	2230	470	39	
5	71	32	22	3570	610	39	T
6	42	9	8	—	—	—	PP
6	36	9	6	1770	350	—	"
7	93	14	11	—	—	32	T
8	107	23	17	3550	780	3	A
9	110	13	7	3450	600	30	D
10	110	—	—	3360	670	38	HR
11	93	8	5	—	—	35	HR
12	88	11	10	2270	650	32	T
13	73	29	13	3570	490	39	T
14	110	—	—	2800	560	39	J
15	93	41	48	3500	540	39	T
16	154	19	18	3640	680	38	T
1	147	44	39	4270	650	39	T
18	119	30	38	3130	630	38	HR
19	165	18	15	—	—	37	HR
19	141	6	5	3840	630	41	
20	119	20	20	3630	680	37	Thyr
21	165	39	29	3940	780	40	HR
22	110	28	22	—	—	35	T
22	122	22	14	—	—	37	
22	128	33	31	3470	610	38	"
23	49	9	6	—	—	35	T
23	48	9	8	—	—	32	
24	105	—	—	3190	500	41	Prol
5	90	—	—	3870	530	42	Prol
26	108	23	31	3110	650	39	HR
27	109	—	—	3350	600	40	HR
28	113	—	—	3780	650	41	Prol
29	108	—	—	3750	700	39	HR
30	76	—	—	3550	870	41	Prol
31	97	—	—	3600	670	41	Prol
32	88	—	—	3300	580	41	Prol
33	171	—	—	3650	690	38	HR
34	77	—	—	3070	470	38	HR
35	77	—	—	3580	630	40	HR
36	66	—	—	3270	500	40	HR
37	116	—	—	3170	560	38	HR
38	82	—	—	3430	500	41	Prol
39	87	5	4	3740	680	38	T
40	110	—	—	4300	680	39	HR
41	128	13	9	3660	700	37	HR

lated to the weight of the child ($r = 0.54 \pm 0.14$ $t_{0.001} = 3.76 < t = 4.28$) on the basis of 38 deliveries (Fig 3) A positive correlation between HPL and placental weight was also observed ($r = 0.64 \pm 0.13$ $t_{0.01} = 2.76 < t = 5.1$ Fig. 4). There was no significant correlation between HPL and pregnancy week in our series of 46 samples examined between 30 and 42 weeks of gestation (Fig 5) The Apgar scores of the children ranged from [illegible] to 10 In the group of mothers having low HPL

Table II *Correlation coefficients (r) and the respective standard errors (s_r) of maternal serum HPL concentration and urinary oestriol excretion, infant and placental weights, and duration of gestation*

number of variable pairs

Oestriol (mg 24 h)	Oestriol (mg/ml)	Infants weight	Placental weight	Pregnancy week
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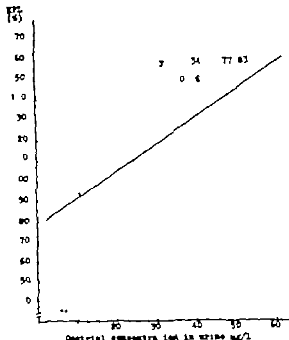


Fig 2 Comparison of serum HPL and urinary oestriol concentration.

DISCUSSION

The radial immunodiffusion method is a simple and reliable technique for the measurement of serum proteins provided that a specific antiserum is available. For clinical use the weakness of the method is that the results cannot be recorded for 48 hours. Our results agree in general with previous observations (Spellacy et al 1966), but we observed a highly significant correlation between HPL and placental weight. That no correlation between HPL and pregnancy week was found is considered to be due to the nature of the pregnancy complications, where continuing placental and foetal development remained questionable. Moreover our findings reflect marked individual variations in serum HPL concentrations between different individuals. The fairly poor correlation between HPL and oestriol may be because of different sources of origin of these hormones. While HPL is a placental product, oestriol excretion depends on the function of the foetoplacental unit. However for clinical use, the results indicate that no definite conclusions about placental function or foetal state are justified on the basis of single HPL determinations from maternal serum. It is possible that marked reduction in maternal HPL concentration might indicate danger to the foetus, but this remains to be established. Large series are necessary to find out the significance of HPL in different pathological conditions of pregnancy

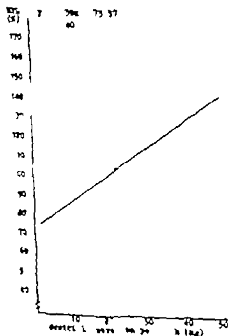


Fig 1 Comparison of serum HPL and urinary oestriol excretion per 24 h

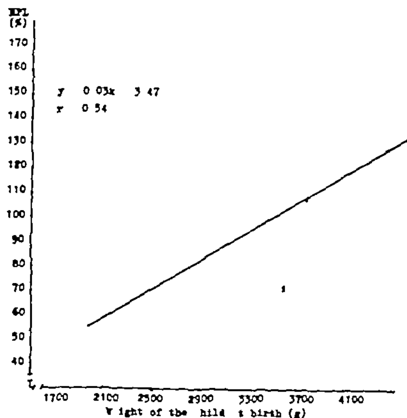
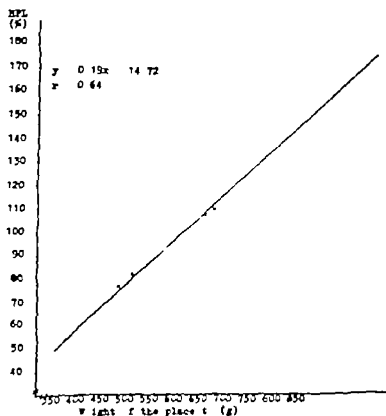


Fig 3 Comparison of serum HPL and birth weight of the child.



F g 4 Comparison of serum HPL and weight of the placenta.

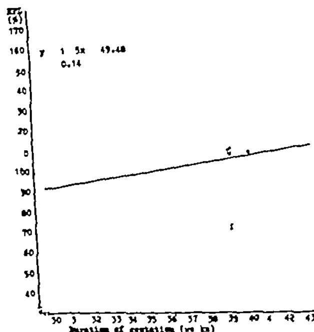


Fig. 5. Comparison of serum HPL and duration of gestation.

REFERENCES

Beck, P., Parker, M. L. & Daughaday, W. H.: Radioimmunologic measurement of human placental lactogen in plasma by a double antibody method during normal and diabetic pregnancies. J Clin Endocrinol Metab *25*: 1457, 1965.

Brown, J. B.: The determination and significance of the natural estrogens. Advances in Clin Chem *3*: 157, 1960.

Mancini, G., Carbonara, A. O. & Heremans, J. F.: Immunochemical quantitation of antigens by single radial immunodiffusion. Immunochemistry 2: 235, 1960.

Sciarra, J. J., Kaplan, S. L. & Grumbach, M.: Localization of anti-human growth hormone serum within the human placenta: Evidence for a human chorionic "Growth Hormone-prolactin". Nature (London) *199*: 1005, 1963.

Spellacy, W. N., Carlson, K. L. & Birk, S. A.: Dynamics of human placental lactogen. Amer J Obstet Gynecol 96: 1164, 1966.

Tallberg, T., Ruoslahti, E. & Ekholm, C.: Immunological studies on human placental proteins and the purification of human placental lactogen. Ann Med exp Fenn 43: 67, 1965.

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EXPERIENCE OF THE USE OF INTRANASAL, BUCCAL AND INTRAVENOUS OXYTOCIN AS METHODS OF INDUCING LABOUR

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Abstract. A clinical trial with intravenous, buccal and intranasal oxytocin used to perform 445 inductions of labour is reviewed. The factors affecting the course, complications and outcome of induction are analysed. A fairly satisfactory result was achieved with all the methods. The intranasal preparation (Partocon IN®) appeared to be a little more effective than the other drugs. Maternal complications were few. Neonatal asphyxia occurred in 5.5 % of cases. Three children (one in each induction group) were lost, one died intrapartum, the other two soon after birth. Intravenous, buccal and intranasal oxytocin are good tools in the obstetrician's hands provided the indications for induction are carefully considered, the patient's readiness for induction is studied carefully, the timing is correct and the procedure is closely supervised.

Induction of labour is a procedure which the modern obstetrician has to consider daily. First he must decide that there is a proper indication for interference and the next step—if conditions are suitable for induction—is to choose the most suitable of several methods.

Page (1943) advanced the idea of administering oxytocin, in the form of Pitocin®, as an intravenous infusion. Much earlier Hofbauer et al (1927) began to instil Pituitrin® solution intranasally and Donaldson (1921) was the first to experiment with the absorption of Pituitrin® from the oral mucosa. All these methods have been modified subsequently, especially after the synthetic production of oxytocin was commenced. The experience gained has been described in many publications. Induction of Labor (1965) by Fields, Greene & Smith is a good summary and provides a comprehensive list of the literature on induction.

In recent years, comparable groups have been collected from one and the same hospital of cases in which induction was performed by two or more methods, e.g. Blair (1964), Maxwell (1964) and Müller & Osler (1967). Comparisons of this kind have been made since 1964 also at Department I of Obstetrics and Gynaecology, Tampere Central Hospital. The results are reviewed here.

MATERIAL AND METHODS

Primary inductions and second attempts at induction, totalling 1 195, performed in 1964–1967 are shown in Table I. The cases included in this series in which primary induction was performed by intravenous Syntocinon® infusion (= S.I.V.), Syntocinon Buccal® tablets (= S.B.) or Partocon IN® solution (= P.I.N.) are outlined in the table. A total of 159 S.I.V. + 121 S.B. and 165 P.I.N. inductions, i.e. 445 inductions in all, are reviewed.

S.I.V. The Syntocinon® preparation of Sandoz was used. 5 I.U. was added to 500 ml of 5 % glucose solution. Infusion was begun at 8–10 drops/min (= 5.3–6.6 mU/min) and increased to 15–20 drops/min (= 9.9–13.2 mU/min). The maximum administered in a single day was 5 I.U.

S.B. Sandoz' Syntocinon Buccal® tablets, one of which contains 100 I.U. of synthetic oxytocin, were used. The maximum dose was 2600 I.U. (100 + 100 + 200 + 200 + 400 + 400 + 600 + 600 I.U. administered at half-hour intervals.

P.I.N. Ferring' Partocon IN® solution was used. The dose was initially according to the manufacturers' instructions: 4 × 5 I.U., 4 × 10 I.U., 4 × 20 I.U. and 4 × 30 I.U. at intervals of 15 min, but the formula was altered fairly soon to an initial dose of 4 × 1 I.U. at intervals of 15 min. The maximum total dosage was 264 I.U.

The rate of oxytocin administration was reduced or therapy continued with a small dose or discontinued in all the methods once good labour was induced and seemed likely to result in delivery.

The stage of effacement and dilatation of the cervix and the height of the presenting part were generally recorded by rectal examination in the morning before the induction was started. Since the end of 1967 routine amnioscopy

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Table IV *Age groups and their relation to outcome of induction*

Percentages in parentheses

Years	P.I.N.	S.B.	S.LV	Total
<19	20 (12)	13 (11)	24 (15)	57 (13)
Success	13 (65)	6 (46)	12 (50)	31 (55)
20–24	50 (30)	41 (34)	46 (29)	137 (31)
Success	37 (74)	29 (71)	27 (59)	93 (68)
25–29	51 (31)	39 (32)	45 (28)	135 (30)
Success	38 (75)	36 (93)	34 (76)	108 (80)
30–34	29 (18)	19 (16)	4 (15)	72 (16)
Success	27 (93)	12 (63)	19 (79)	58 (81)
35–39	10 (6.0)	7 (5.8)	11 (6.9)	28 (6.3)
Success	10 (100)	5 (72)	7 (64)	22 (79)
≥40	5 (3.0)	2 (1.7)	9 (5.7)	16 (3.6)
Success	5 (100)	2 (100)	7 (78)	14 (88)
	165	121	159	445

Induction was classified as successful if delivery took place within 48 hours of the first oxytocin dose, even if Caesarean section proved necessary for one reason or another after regular labour pains had commenced.

RESULTS

The results are summarised in Table III. Induction was successful ("positive") in three out of four cases on average. The best result (79 %) was obtained in the P.I.N. group and the poorest (67 %) in the S.LV. group. The percentage of successful inductions in the S.B. material was 75. Turnbull & Anderson (1968) suggested that induction should be regarded as failure if parturition had to be terminated by Caesarean section because of (*a*) uterine spasm, (*b*) symptoms suggestive of foetal asphyxia or (*c*) slow progress of labour. If this series is assessed by these criteria, the number of successful inductions in the P.I.N. group is 127 (77 %), in the S.B. group 90 (75 %) and in the S.LV. group 100 (63 %).

The average P.I.N. dosage was 175 I.U. and in the cases of successful induction 154 I.U. The corresponding S.B. dosages were 1916 I.U. and 1730 I.U. The average S.LV. dosage was 3.8 I.U. for the total series and for the successful inductions.

The distribution of the series into *age groups* and the corresponding success rates for induction are shown in Table IV. There are no significant differences in the age distribution. The outcome was poorest, regardless of the oxytocin preparation given, in the youngest group which naturally contained the highest number of primigravidas. However P.I.N. gave relatively good result (65 %) compared with other preparations.

Table V presents the relation of *parity* to the outcome of the inductions performed. Induction failed distinctly more often in primi- than in multigravidas. It should be noted that primigravidas were most numerous in the S.LV. group (50 %) and that the induction was successful in only about half of these cases. The proportion of primigravidas was unfortunately unequal in the three groups. It was 40 % in the S.B. and 45 % in the P.I.N. group.

Table V *Relation of parity to outcome of induction*

Percentages in parentheses

	P.I.N.	S.B.	S.LV	Total
Primigravidae	74 (45)	45 (40)	79 (50)	201 (45)
Success	49 (66)	30 (67)	42 (53)	121 (60)
Multigravidae	91 (55)	73 (60)	80 (50)	244 (55)
Success	81 (89)	60 (82)	64 (80)	205 (84)
	165	121	159	445

11 [illegible]

Table I. *Methods and number of inductions in 1964–1967*

Year	1964	1965	1966	1967
Deliveries, total	1929	2047	2122	2230
Amniotomy	—	171	39	11
Syntocinon Buccal* (S.B.)				
Primary	—		121	7
Secondary	—		10	11
Syntocinon Intravenous* (S.I.V.)				
Primary	126	33	107	91
Secondary	183	22		57
Partocon IN* (P.I.N.)				
Primary	—	—	—	165
Secondary	—	—	—	41
Inductions, total	309	226	277	383
Inductions, per cent of deliveries	16%	11%	13%	17%

has been performed before induction of labour The foetal heart rate and the mother's condition were followed at intervals of 15–30 min, and more frequently when disturbances were observed.

Rupture of the membranes, if done at all, was usually performed only when labour had definitely begun. The membranes had ruptured spontaneously in 19 cases (4.3% of the total series) but, in these cases there was no evidence of labour when the induction was started 4 hours later There were no significant differences between the different induction groups in this respect. The membranes were ruptured in some cases at the same time as the administration of the oxytocin preparation was begun. In the S.B. group a little more frequently (15 patients = 12%), in the S.I.V group more rarely (10

Table II *Indications for induction of labour*

Percentages in parentheses

	P.I.N.	S.B.	S.I.V.	Total
Postmaturity	76 (46)	55 (46)	65 (41)	196 (44)
Postmaturity radiographic evidence	18 (11)	11 (9.1)	19 (12)	48 (11)
Pre-eclampsia	55 (33)	36 (30)	74 (47)	165 (37)
Premature rupture of membranes	6 (3.6)	4 (3.3)	11 (6.9)	21 (4.7)
Diabetes mellitus	—	—	1 (0.6)	1 (0.2)
Intrauterine foetal death	—	2 (1.7)	1 (0.6)	3 (0.7)
Previous large babies	9 (5.5)	5 (4.1)	3 (1.9)	17 (3.8)
Previous complications of delivery	41 (25)	35 (29)	37 (23)	113 (25)
Sign of pre-eclampsia at visits to ante-natal clinics	55 (33)	47 (39)	87 (55)	189 (43)
Other reasons	49 (30)	3 (?6)	40 (25)	1 1 (?7)

Table III. *Results of inductions of labour*

Percentages in parentheses
I.D.T = Induction Delivery Time

	P.I.N.	S.B.	S.I.V.	To
Negative				
No contractions in 48 hours	17 (10)	23 (19)	28 (17)	68
Negative				
Contractions but no delivery in 48 hours	18 (11)	8 (6.6)	25 (16)	51 (
Negative, total	35 (21)	31 (25)	53 (33)	119 (
Positive				
I.D.T. less than 24 hours	120 (73)	84 (70)	96 (60)	300 (
Positive				
I.D.T 24–48 hrs	10 (6.1)	6 (5.0)	10 (6.3)	26 (
Positive total	130 (79)	90 (75)	106 (67)	326
Inductions, total	165	121	159	445

patients = 6.3%) and in the P.I.N group in a few only (8 patients = 4.9%). It is, of course, possible this concurrent surgical induction may have affected end results to some extent.

When induction failed on the first day it was not tempted again for 48 hours, and then usually with same method, but with a change to Syntocinon* Infu in a few cases and especially at the third attempt. tempts at induction were repeated more than twice exceptional cases only (1.6%).

The indications f induction of labour are giver Table II. They were similar in the different groups, the role of toxaemia was significantly greater in S.I.V group (47%) compared with the P.I.N. and groups (33 and 30% respectively). The main indicati included among other reasons were latent diabe anaemias of pregnancy elderly primigravida, protrac latent phase f prelabour and twin pregnancy

Postmaturity was a relatively frequent indication induction. If the menstrual history was regarded reliable pregnancy was classified as postmature if 10 more days had elapsed from the date of confinem calculated on the basis of menstruation. Some pregnanc were considered to be postmature on the strength f t radiologist report although they were less than 10 d. overdue by dates.

If the only evidence of toxaemia was the entries the patient ante-natal clinic record, it wa not regard as an indication for induction. It was definitely mo common t decide on induction on the strength of mo than one indication (the number of indications per i duction in the whole series wa 1.96).

A previous large baby and a history f complicate delivery were not regarded by themselves as sufficier indications for induction.

Table IV *Age groups and their relation to outcome of induction*

Percentages in parentheses

Years	P.I.N.	S.B.	S.I.V.	Total
<19	20 (12)	13 (11)	24 (15)	57 (13)
Success	13 (65)	6 (46)	12 (50)	31 (55)
20–24	50 (30)	41 (34)	46 (29)	137 (31)
Success	37 (74)	29 (71)	27 (59)	93 (68)
25–29	51 (31)	39 (32)	45 (28)	135 (30)
Success	38 (75)	36 (93)	34 (76)	108 (80)
30–34	29 (18)	19 (16)	24 (15)	72 (16)
Success	27 (93)	12 (63)	19 (79)	58 (81)
35–39	10 (6.0)	7 (5.8)	11 (6.9)	28 (6.3)
Success	10 (100)	5 (72)	7 (64)	22 (79)
≥40	5 (3.0)	2 (1.7)	9 (5.7)	16 (3.6)
Success	5 (100)	2 (100)	7 (78)	14 (88)
	165	121	159	445

Induction was classified as successful if delivery took place within 48 hours of the first oxytocin dose, even if Caesarean section proved necessary for one reason or another after regular labour pains had commenced.

RESULTS

The results are summarized in Table III. Induction was successful ("positive") in three out of four cases on average. The best result (79%) was obtained in the P.I.N. group and the poorest (67%) in the S.I.V. group. The percentage of successful inductions in the S.B. material was 75. Turnbull & Anderson (1968) suggested that induction should be regarded as a failure if parturition had to be terminated by Caesarean section because of (*a*) uterine spasm, (*b*) symptoms suggestive of foetal asphyxia or (*c*) slow progress of labour. If this series is assessed by these criteria, the number of successful inductions in the P.I.N. group is 127 (77%), in the S.B. group 90 (75*) and in the S.I.V. group 100 (63%).

The average P.I.N. dosage was 175 I.U. and in the cases of successful induction 154 I.U. The corresponding S.B. dosages were 1916 I.U. and 1730 I.U. The average S.I.V. dosage was 3.8 I.U. for the total series and for the successful inductions.

The distribution of the series into *age groups* and the corresponding success rates for induction are shown in Table IV. There are no significant differences in the age distribution. The outcome was poorest, regardless of the oxytocin preparation given, in the youngest group which naturally contained the highest number of primigravidas. However, P.I.N. gave a relatively good result (65*) compared with other preparations.

Table V presents the relation of *parity* to the outcome of the inductions performed. Induction failed distinctly more often in primi- than in multigravidas. It should be noted that primigravidas were most numerous in the S.I.V. group (50*) and that the induction was successful in only about half of these cases. The proportion of primigravidas was unfortunately unequal in the three groups: it was 40* in the S.B. and 45% in the P.I.N. group.

Table V *Relation of parity to outcome of induction*

Percentages in parentheses

	P.I.N.	S.B.	S.I.V.	Total
Primigravidae	74 (45)	48 (40)	79 (50)	201 (45)
Success	49 (66)	30 (62)	42 (53)	121 (60)
Multigravidae	91 (55)	73 (60)	80 (50)	244 (55)
Success	81 (89)	60 (82)	64 (80)	205 (84)
	165	121	159	445

Table VI *Relation of period of gestation to outcome of induction*

Percentages in parentheses

Gestat. week	P I N	S.B.	S.I V	Total
≤38	2 (1.2)	5 (4 1)	15 (9.5)	22 (5 0)
Success	2 (100)	3 (60)	11 (74)	16 (73)
39–40	36 (22)	35 (29)	33 (21)	104 (23)
Success	31 (86)	25 (71)	2. (67)	78 (75)
41–42	85 (52)	53 (44)	69 (43)	707 (46)
Success	65 (76)	44 (83)	45 (65)	154 (75)
≥43	41 (25)	28 (23)	41 (26)	110 (25)
Success	32 (78)	18 (64)	28 (68)	78 (71)
Uncertain	1 (0 6)	—	1 (0.6)	2 (0.5)
Success	—	—	—	—
	165	121	159	445

Table VII *Duration of labour*

Percentages in parentheses

Hours	P.I N	S B	S I V	Total
Less than 6	66 (51)	48 (53)	37 (35)	151 (46)
6–12	48 (37)	27 (30)	45 (42)	170 (37)
More than 12	16 (12)	15 (17)	24 (23)	55 (17)
	130	90	106	326

The period of gestation did not appear to have a definite effect on the outcome of induction, as can be seen from Table VI The distribution was somewhat uneven deliveries before the 39th week being most numerous in the S.I V group On the other hand, postmaturity occurred equally in all the investigation groups. 23–26 of the pregnancies had reached the 43rd week.

The duration of labour with the different methods of induction is presented in Table VII Half of the deliveries in the P I N and S.B groups approximately a third in the S.I V group curred after less than 6 hours of labour

It is common knowledge that induction is ea when *the degree of cervical "ripeness* incre. and *the presenting part* descends. The sam. servation was made in the present series, *results are given in Tables VIII IX and X.* station of the presenting part was above the l of the ischial spines in 8–9 cases out of 10 all the groups when induction was started. It *often difficult to be certain about the degree* effacement of the cervical canal and the evaluat was in fact uncertain in this respect in roug four out of 10 cases in the S.B and S I V gro and in 32 % of the P I.N group (*Table X*). I certainty about the dilatation of the external c vical os was greatest in the S I V group (25 the proportion of "uncertain" cases was alm equal in the other two groups. 7 4 and 7.5 Induction was generally successful if the cervi

Table VIII *Relation of station of presenting part (immediately prior to induction) to outcome of induction*

Percentages in parentheses

Station in relation to ischial spines	P I N	S B.	S.I.V	Total
Higher than 2 cm	42 (25)	42 (35)	36 (23)	120 (27)
Success	3. (76)	27 (64)	19 (53)	78 (65)
Between 0 and cm	103 (63)	57 (47)	100 (63)	260 (59)
Success	81 (79)	44 (77)	74 (74)	199 (77)
Lower than 0	11 (6 7)	12 (9 9)	9 (5 7)	3 (7)
Success	10 (91)	11 (9)	6 (67)	27 (85)
Uncertain	9 (5 6)	10 (8.3)	14 (8 8)	33 (7 4)
Success	7 (78)	8 (80)	7 (50)	.. (67)
	165	1 1	159	445

Table IX. *Relation of dilatation of cervix (immediately prior to induction) to outcome of induction*

Percentages in parentheses

Dilatation	P.I.N.	S.B.	S.I.V.	Total
Less than 2 cm	42 (26)	38 (31)	46 (29)	126 (28)
Success	25 (60)	20 (53)	20 (44)	65 (52)
2 cm or more	111 (67)	74 (61)	73 (46)	258 (58)
Success	95 (86)	63 (85)	59 (81)	217 (84)
Uncertain	12 (7.4)	9 (7.5)	40 (25)	61 (14)
Success	10 (83)	7 (78)	27 (68)	44 (72)
	165	121	159	445

Table X. *Relation of cervical effacement (immediately prior to induction) to outcome of induction*

Percentages in parentheses

Degree	P.I.N.	S.B.	S.I.V.	Total
Less than 50 %	7 (4.2)	6 (5.0)	3 (1.9)	16 (3.6)
Success	4 (57)	4 (67)	—	8 (50)
50–80 %	37 (23)	21 (17)	46 (29)	104 (23)
Success	24 (65)	10 (47)	28 (61)	62 (60)
Complete	68 (41)	40 (33)	43 (27)	151 (34)
Success	57 (84)	37 (93)	34 (79)	128 (85)
Uncertain	53 (32)	54 (45)	67 (42)	174 (39)
Success	45 (85)	39 (72)	44 (66)	128 (74)
	165	121	159	445

Table XI. *Relation of artificial or spontaneous rupture of membranes to outcome of induction and duration of labour*

Percentages in parentheses
S.R.M. Spontaneous Rupture of Membranes
A.R.M. Artificial Rupture of Membranes
D.L. Duration of Labour

State of membranes	P.I.N.	S.B.	S.I.V.	Total
Remained intact, induction unsuccessful	34 (20)	30 (25)	50 (31)	114 (26)
S.R.M. no labour after 24 hours	4 (2.4)	6 (5.0)	9 (5.7)	19 (4.3)
Induction successful	3	6	8	17
D.L. less than 6 h	—	1 (17)	5 (63)	6 (35)
A.R.M. simultaneously with start of induction	8 (4.9)	15 (12)	10 (6.3)	33 (7.4)
Induction successful	8	15	10	33
D.L. less than 6 h	8 (100)	11 (74)	5 (50)	24 (73)
A.R.M. after estab. of contraction pattern	54 (33)	43 (36)	62 (39)	159 (36)
Induction successful	54	42	62	158
D.L. less than 6 h	4 (45)	18 (43)	18 (29)	60 (38)
A.R.M. after complete cervical dilatation	10 (6.0)	10 (8.3)	3 (1.9)	23 (5.2)
Induction successful	10	10	3	23
D.L. less than 6 h	5 (50)	6 (60)	1 (33)	12 (52)
S.R.M. during labour	53 (32)	17 (14)	24 (15)	94 (21)
Induction successful	53	17	22	92
D.L. less than 6 h	29 (55)	12 (71)	7 (32)	48 (52)
Remained intact until Caesarean section	2 (1.2)	—	1 (0.6)	3 (0.7)
	165	121	159	445

Table XII *Method of delivery*

Percentages in parentheses

	P.I.N	S.B.	S.I.V	Total
Spontaneous	149 (90)	109 (90)	133 (84)	391 (88)
Primigravidae	61	41	63	165 (43)
Multigravidae	88	68	70	2.6 (57)
Caesarean section	9 (5.5)	9 (7.5)	13 (8.2)	31 (7.0)
Primigravidae	8	6	10	24 (78)
Multigravidae	1	3	3	7 (22)
Vacuum extractor or forceps	4 (2.4)	2 (1 7)	5 (3 1)	11 (2.5)
Primigravidae	4	1	5	10 (91)
Multigravidae	—	1	—	1 (9 0)
Breech delivery	3 (1.8)	1 (0.8)	8 (5 0)	12 (2.7)
Primigravidae	1	—	1	2 (17)
Multigravidae		1	7	10 (83)
	165	121	159	445

canal was effaced completely and the external os was open 2 cm or more. This was the case in 46 cases out of 52 (89%) in the P I.N group, in 32 out of 33 cases (97%) in the S.B group and in the S I V group in all 25 cases in which the cervix satisfied the above criteria.

Table XI shows the relation of artificial or spontaneous *rupture of the membranes* to the outcome of induction and the *duration of labour* Labour appeared to progress more rapidly if the membranes were ruptured at the time of the oxytocin induction Combined surgical and oxytocin induction was used intentionally only in exceptional cases, in 7 4% of the total series There were some differences in this respect between the various groups. Even if all these cases are excluded, the percentage of successful inductions was 78 in the P I N., 74 in the S.B and 65 in the S.I V group. These results do not differ significantly from those in the complete series (Table III)

Tables XII XIII and XIV illustrate *the course of delivery* It was spontaneous in 9 out of cases in the P I.N and S.B groups and in 8 of the S.I V group The corresponding C section rates were 5.5 7.5 and 8.2% u primary induction was unsuccessful the freque of sections rose to a fairly high figure (T XIV) 23% in the S.B and 11% in the groups. The majority of the patients whose livery ended operatively were primigravidas. of the patients with Caesarean section and 9 of the patients with vacuum extractor or delivery

All indications for operative delivery are in Table XV Postmaturity and toxaemia were course, common indications for induction The decision to undertake Caesarean section not prompted by mere failure of induction distress and uterine inertia were the comm additional considerations. No significant dif ences were established between the various gro as shown in Table XV Seven cases displa relative cephalopelvic disproportion during

Table XIII *Method of delivery of cases with successful primary induction*

Percentages in parentheses

	P I N	S.B.	S.I.V	Total
Spontaneous	120 (93)	87 (97)	90 (85)	297 (91)
Caesarean section	5 (3.8)	(2.2)	7 (6.6)	14 (4.3)
Vacuum extractor or forceps	2 (1.5)	–	4 (3.8)	6 (1 8)
Breech delivery	3 (2.3)	1 (1 1)	5 (4.7)	9 (2.8)
	130	90	106	326

Table XIV *Method of delivery of cases with successful primary induction*

Percentages in parentheses

	P I N	S B	S I V	Total
Spontaneous	29 (83)	22 (71)	43 (81)	94 (7
Caesarean section	4 (11)	7 (23)	6 (11)	17 (14)
Vacuum extractor or forceps	2 (5 7)	2 (6 5)	1 (1 9)	5 (4 2
Breech delivery			3 (5 7)	3 (2 5
	35	31	53	119

Table XV. *Indications for operative delivery, associated asphyxia of newborn and neonatal mortality*

	P.I.N.		S.B.		S.I.V.		
	Caesarean section (9)	V.E. or forceps (4)	Caesarean section (9)	V.E. or forceps (2)	Caesarean section (13)	V.E. or forceps (5)	Total
Postmaturity	5	—	4	—	6	—	15
Pre-eclampsia	3	—	2	—	8	—	13
Foetal distress	3	2	2	1	3	1	12
Exhaustion of mother	1	—	2	1	1	1	6
Inertia	3	2	2	1	4	2	14
Cephalopelvic disproportion	2	—	2	—	3	—	7
Elderly primigravida	—	—	1	—	1	—	2
Abruptio placentae	—	—	—	—	1	—	1
Prolapsed cord	1	—	—	—	1	—	2
Leiomyomata	1	—	2	—	—	—	3
Malignant myopia	—	—	—	—	—	1	1
Asphyxia of newborn	2	1	1	—	3	—	7
Neonatal mortality	1	—	—	—	1	—	2

course of labour. Induction would obviously have been abandoned in these cases had the disproportion been diagnosed originally. The incidence of asphyxia was highest in all the groups when operative delivery proved necessary. Three of the six asphyxiated infants in the P.I.N. group, three out of 11 in the S.I.V. and one out of eight in the S.B. group had operative deliveries.

Table XVI presents the cases in which *post partum haemorrhage* was 500 g or more. No significant differences were established between the groups.

Maternal complications are seen in Table XVII. The number was small and there seemed to be no distinct differences between the groups. However, P.I.N. seems to cause more (4.–%) hypertonic contractions of long duration than S.B. and S.I.V. (0.8 and 1.9). This particular complication was managed in every case by reducing the dose and/or lengthening the interval between doses without having to discontinue induction. There was no maternal mortality.

Table XVI. *Postpartum haemorrhage*

Percentages in parentheses

Amount in grams	P.I.N.	S.B.	S.I.V.	Total
Less than 500	154 (94)	116 (96)	151 (95)	421 (95)
500–900	9 (5.5)	3 (2.5)	5 (3.1)	17 (3.8)
More than 900	2 (1.[illegible])	2 (1.7)	3 (1.9)	7 (1.6)
	165	121	159	445

The *birth weight* by groups is presented in Table XVIII. The babies of the S.I.V. group were a little smaller on average. Probable reasons for this were that this group contained the highest number of primigravidas, all the twin pregnancies and toxaemia was more frequently the indication for induction in this group.

Findings indicative of foetal distress were fairly common (Table XIX). The incidence of these signs in cases where the baby showed no evidence of asphyxia at birth was 13% in the total series, lowest (10%) in the P.I.N. group and highest (15%) in the S.I.V. group.

Table XX lists the cases of genuine neonatal asphyxia. One child was lost in each group, in the S.B. group intrapartum and in the other groups during the first week of life.

Table XVII. *Maternal complications*

Percentages in parentheses

	P.I.N.	S.B.	S.I.V.	Total
Uterine hypertonus	7 (4.2)	1 (0.8)	3 (1.9)	11 (2.5)
Retained placenta	1 (0.6)	2 (1.7)	6 (3.8)	9 (2.0)
Atony of uterus		2 (1.7)		2 (0.5)
Lochiometra	8 (4.9)	5 (4.1)	11 (6.9)	24 (5.5)
Puerperal endometritis	3 (1.8)	4 (3.3)	5 (3.1)	12 (2.7)
Other infections	4 (2.4)	3 (2.5)	1 (0.6)	8 (1.8)
Other complications*	2 (1.2)	(1.7)	6 (3.8)	10 (2.3)

* P.I.N.: Suspected listeriosis (1), hydramnios (1).
S.B.: Vaginal tear (1), superficial thrombophlebitis (1).
S.I.V.: Phlebothrombosis (2), symphysiolysis (2), third degree perineal laceration (1), sudden collapse (1).

Table XII *Method of delivery*

Percentages in parentheses

	P.I.N.	S.B.	S.I.V.	Total
Spontaneous	149 (90)	109 (90)	133 (84)	391 (88)
Primigravidae	61	41	63	165 (43)
Multigravidae	88	68	70	226 (57)
Caesarean section	9 (5.5)	9 (7.5)	13 (8.2)	31 (7.0)
Primigravidae	8	6	10	4 (78)
Multigravidae	1	3	3	7 (22)
Vacuum extractor or forceps	4 (2.4)	2 (1.7)	5 (3.1)	11 (2.5)
Primigravidae	4	1	5	10 (91)
Multigravidae	—	1	—	1 (9.0)
Breech delivery	3 (1.8)	1 (0.8)	8 (5.0)	12 (2.7)
Primigravidae	1	—	1	2 (17)
Multigravidae	2	1	7	10 (83)
	165	121	159	445

canal was effaced completely and the external os was open 2 cm or more. This was the case in 46 cases out of 52 (89%) in the P.I.N. group in 32 out of 33 cases (97%) in the S.B. group and in the S.I.V. group in all 25 cases in which the cervix satisfied the above criteria.

Table XI shows the relation of artificial or spontaneous *rupture of the membranes* to the outcome of induction and the *duration of labour*. Labour appeared to progress more rapidly if the membranes were ruptured at the time of the oxytocin induction. Combined surgical and oxytocin induction was used intentionally only in exceptional cases, in 7.4% of the total series. There were some differences in this respect between the various groups. Even if all these cases are excluded, the percentage of successful inductions was 78 in the P.I.N., 74 in the S.B. and 65 in the S.I.V. group. These results do not differ significantly from those in the complete series (Table III).

Tables XII, XIII and XIV illustrate *the course of delivery*. It was spontaneous in 9 out of 10 cases in the P.I.N. and S.B. groups and in 84 of the S.I.V. group. The corresponding Caesarean section rates were 5.5, 7.5 and 8.2%. When primary induction was unsuccessful the frequency of sections rose to a fairly high figure (Table XIV) 23% in the S.B. and 11 in the other groups. The majority of the patients whose delivery ended operatively were primigravidae: 78% of the patients with Caesarean section and 91 of the patients with vacuum extractor or forceps delivery.

All indications for operative delivery are shown in Table XV. Postmaturity and toxaemia were, of course, common indications for induction too. The decision to undertake Caesarean section was not prompted by mere failure of induction: foetal distress and uterine inertia were the commonest additional considerations. No significant differences were established between the various groups as shown in Table XV. Seven cases displayed relative cephalopelvic disproportion during the

Table XIII *Method of delivery of cases with successful primary induction*

Percentages in parentheses

	P.I.N.	S.B.	S.I.V.	Total
Spontaneous	120 (93)	87 (97)	90 (85)	297 (91)
Caesarean section	5 (3.8)	2 (2.2)	7 (6.6)	14 (4.3)
Vacuum extractor or forceps	2 (1.5)	–	4 (3.8)	6 (1.8)
Breech delivery	3 (2.3)	1 (1.1)	5 (4.7)	9 (2.8)
	130	90	106	326

Table XIV *Method of delivery of cases with unsuccessful primary induction*

Percentages in parentheses

	P.I.N.	S.B.	S.I.V.	Total
Spontaneous	29 (83)	22 (71)	43 (81)	94 (79)
Caesarean section	4 (11)	7 (23)	6 (11)	17 (14)
Vacuum extractor or forceps	2 (5.7)	2 (6.5)	1 (1.9)	5 (4.2)
Breech delivery			3 (5.7)	3 (2.5)
	35	31	53	119

Table XV *Indications for operative delivery associated asphyxia of newborn and neonatal mortality*

	P.I.N.		S.B.		S.I.V		
	Caesarean section (9)	V.E. or forceps (4)	Caesarean section (9)	V.E. or forceps (2)	Caesarean section (13)	V.E. or forceps (5)	Total
Postmaturity	5	—	4	—	6	—	15
Pre-eclampsia	3	—	2	—	8	—	13
Foetal distress	3	2	2	1	3	1	12
Exhaustion of mother	1	—	2	1	1	1	6
Inertia	3	2	2	1	4	2	14
Cephalopelvic disproportion	2	—	2	—	3	—	7
Elderly primigravida	—	—	1	—	1	—	2
Abruptio placentae	—	—	—	—	1	—	1
Prolapsed cord	1	—	—	—	1	—	2
Leiomyomata	1	—	2	—	—	—	3
Malignant myopia	—	—	—	—	—	1	1
Asphyxia of newborn	2	1	1	—	3	—	7
Neonatal mortality	1	—	—	—	1	—	2

course of labour. Induction would obviously have been abandoned in these cases had the disproportion been diagnosed originally. The incidence of asphyxia was highest in all the groups when operative delivery proved necessary. Three of the [illegible] asphyxiated infants in the P.I.N. group, three out of 11 in the S.I.V. and one out of eight in the S.B. group had operative deliveries.

Table XVI presents the cases in which *post partum haemorrhage* was 500 g or more. No significant differences were established between the groups.

Maternal complications are seen in Table XVII. The number was small and there seemed to be no distinct differences between the groups. However P.I.N. seems to cause more (4.2%) hypertonic contractions of long duration than S.B. and S.I.V. (0.8 and 1.9%). This particular complication was managed in every case by reducing the dose and/or lengthening the interval between doses without having to discontinue induction. There was no maternal mortality.

Table XVI *Postpartum haemorrhage*

Percentages in parentheses

Amount in grams	P.I.N.	S.B.	S.I.V.	Total
Less than 500	154 (94)	116 (96)	151 (95)	421 (95)
500–800	9 (5.5)	3 (2.5)	5 (3.1)	17 (3.8)
More than 800	2 (1.2)	2 (1.7)	3 (1.9)	7 (1.6)
	165	121	159	445

The *birth weight* by groups is presented in Table XVIII. The babies of the S.I.V. group were a little smaller on average. Probable reasons for this were that this group contained the highest number of primigravidas, all the twin pregnancies and toxaemia was more frequently the indication for induction in this group.

Findings indicative of foetal distress were fairly common (Table XIX). The incidence of these signs in cases where the baby showed no evidence of asphyxia at birth was 13% in the total series, lowest (10%) in the P.I.N. group and highest (15%) in the S.I.V. group.

Table XX lists *the cases of genuine neonatal asphyxia*. One child was lost in each group, in the S.B. group intrapartum and in the other groups during the first week of life.

Table XVII. *Maternal complications*

Percentages in parentheses

	P.I.N.	S.B.	S.I.V.	Total
Uterine hypertonus	7 (4.2)	1 (0.8)	3 (1.9)	11 (2.5)
Retained placenta	1 (0.6)	2 (1.7)	6 (3.8)	9 (2.0)
Atony of uterus		2 (1.7)		2 (0.5)
Lochiometra	8 (4.9)	5 (4.1)	11 (6.9)	24 (5.5)
Puerperal endometritis	3 (1.8)	4 (3.3)	5 (3.1)	12 (2.7)
Other infections	4 (2.4)	3 (2.5)	1 (0.6)	8 (1.8)
Other complications	2 (1.2)	2 (1.7)	6 (3.8)	10 (2.3)

P.I.N. Suspected listeriosis (1), hydramnios (1).
S.B. Vaginal tear (1), superficial thrombophlebitis (1).
S.I.V. Phlebothrombosis (2), symphysiolysis (2), third degree perineal laceration (1), sudden collapse (1).

Table XVIII *Birth weight*

Percentages in parentheses

Grams	P I N	S.B.	S.I V	Total
< 1499	—	1 (0.8)	2 (1.2)	3 (0.7)[a]
1500–2499	—	1 (0.8)	2 (1.2)	3 (0.7)
2500–3499	44 (27)	36 (30)	65 (38)	145 (32)
3500–4499	110 (67)	75 (61)	96 (56)	281 (62)
≥ 4500	11 (6.7)	8 (6.6)	5 (2.9)	24 (5.3)
	165	121	170	456
(Twin pregnancy	—	—	11	11)

[a] Foetuses died antenatally during 2nd trimester

Table XIX *Signs of foetal distress without neonatal asphyxia*

Percentages in parentheses

	P I.N	S.B	S.I.V	Total
Abnormal foetal heart rate[a]	1 (0.6)	5 (4.1)	10 (6 3)	16 (3 6)
Meconium in amniotic fluid	15 (9 1)	8 (6.6)	11 (6.9)	34 (7 7)
Abnormal foetal heart rate & meconium in amniotic fluid	1 (0.6)	(1 7)	3 (1 9)	6 (1 4)
	17 (10)	15 (12)	24 (15)	56 (13)

[a] Heart rate ≥ 160/min or < 110/min or irregular

Case 1 A gravida III aged 33 whose previous deliveries had been nine and 10 years earlier Induction had been performed on both occasions but the indication for it was not known. On this occasion labour was induced in the 41st week of gestation f r toxaemia and suspected rupture f the membranes. The patient was given 2600 I.U of S.B. tablets without effect. A second induction, likewise with 2600 I.U of S.B. tablets, was performed n e 48 hours. Weak contractions were induced, but disappeared for almost 4 hours. Labour then started, the mother s blood pressure rose to 160/110. Foetal heart

Table XX. *Neonatal asphyxia and intrapartum or neonatal mortality with or without signs of foetal distress, method of delivery*

Percentages in parentheses
N B. 3 cases f a tenatal foetal deaths not included

	P I N	S.B.	S.I V	Total
Asphyxiated baby no signs of foetal distress noticed	4 (2.4)	4 (3.3)	5 (3 1)	13 (2.9)
Spontaneous delivery	2	4	3	9 (69)
Caesarean section	1	—	1	2 (15)
Breech delivery	1	—	1	2 (15)
Asphyxiated baby abnormal foetal heart rat	—	2 (1 7)	3 (1.9)	5 (1 1)
Spontaneous delivery	—	1	1	2 (40)
Caesarean section	—	1	1	2 (40)
Breech deli ery	—	—	1	1 (20)
Asphyxiated baby meconium in amniotic fluid	—	1 (0.8)	1 (0 6)	2 (0 5)
Spontaneous delivery	—	1	1	2 (100)
Asphyxiated baby abnormal foetal heart rate, meconium n amniotic fluid	1 (0 6)	—	1 (0.6)	2 (0.5)
Vacuum extractor	1	—	—	1 (50)
Breech delivery	—	—	1	1 (50)
Intrapartum death (see Case Report)	—	1 (0 8)	—	1 (0 22)
Spo taneous delivery	—	1	—	1 (100)
Neonatal death (see Case Report)	1 (0 6)	—	1 (0.6)	2 (0.5)
Caesarean section	1	—	1	2 (100)
Asphyxia	5 (3 0)	7 (5 8)	10 (5 9)	2_ (4 8)
Deaths	1 (0 6)	1 (0 8)	1 (0 6)	3 (0 66)
Spontaneous delivery		7	5	14 (56)
Caesarean section		1	3	6 (4)
Vacuum extractor	1	—	—	1 (4 0)
Breech deli ery	1	—	3	4 (16)

sounds ceased 75 min antepartum. The membranes did not rupture until the cervix was completely dilated, the amniotic fluid was green. The baby was stillborn, birth weight 3,540 g. The autopsy diagnosis was aspiration of amniotic fluid.

Case A primigravida aged 26 had an induction performed in the 43rd week of gestation for postmaturity. She was given 264 I.U. of Partocon IN® solution. Labour started, but green amniotic fluid was observed at an early stage and Caesarean section was performed. The infant weighed 3,000 g, had an Apgar score of 3–7 and died at the age of 31 hours. The autopsy diagnosis was intrauterine neonatal pneumonia, aspiration of amniotic fluid, pulmonary hyaline membrane. The maternal listeria antibodies were elevated and, according to the pathologist, "listeriosis towards the end of pregnancy" was involved.

Case 3 A gravida V aged 27 who had a history of threatened abortion in the sixth month of gestation during her third pregnancy. The previous pregnancies were otherwise normal. The membranes ruptured spontaneously in the 34th week of gestation. There was associated bleeding which appeared to be foetal according to Apt test. Syntocinon® instillation was commenced: the patient received *only 0.6* in all. There was more profuse bleeding after active labour started and Caesarean section was performed for suspected abruptio placentae. The baby birth weight was 1,455 g, Apgar score 1 2, death ensued in 4 hours. Rupture of the marginal sinus was found in the placenta and the infant' autopsy diagnosis was pulmonary immaturity, incomplete pulmonary hyaline membrane, intra-alveolar and interstitial pulmonary haemorrhage, petechial haemorrhage of the epicardium, haemoperitoneum and immaturity.

(N. B. In the S.I.V. group another three inductions were performed during the second trimester of gestation on account of the death of the foetus.)

It seems that induction contributed to the foetal death only in case 1.

True asphyxia when the newborn was awarded an Apgar score of 7 or less and which had been preceded in roughly half of the cases by pathological changes in the heart sounds and/or meconium in the amniotic fluid was a little less frequent in the P.I.N. group than in the other groups.

Caesarean section was resorted to in about one quarter of these cases, mostly because of suspected asphyxia or uterine inertia. The incidence of breech presentations was also relatively high (16%). The total number of asphyxial complications was rather low in view of the fact that pregnancy was regarded as being pathological in every case in which induction was undertaken.

COMMENTS

Partocon IN®

Compared with the other two oxytocin preparations Partocon IN® induction gave a slightly better result and recourse to operative delivery was required less often. The experience gained in this hospital is thus somewhat at variance with that reported by Müller & Osler (1967) who gave 60 as the percentage of successful inductions by this method. It is possible that the longer interval (20 min) between individual doses diminished the efficiency of their method. In Borglin's (1962) series, on the other hand, induction was successful in 88.5% of cases, but the membranes had ruptured in about two-thirds of his patients and uterine contractions had already begun spontaneously in 55%.

Eight of the 41 patients in the P.I.N. group had a history of complications in previous deliveries necessitating operative procedures: three Caesarean sections, four vacuum extractions and one forceps delivery. This time all these patients were delivered normally. It thus seems possible that induction reduced the need for operative deliveries.

Partocon® was found by van Gent, Eskes & Seelen (1967) to cause increased intrauterine pressure because of myometrial polysystole or hypertonus in six out of a group of 22 patients. Both forms of overactivity also occurred spontaneously. It seems possible that oxytocin may cause such a complication whichever way it is administered. These authors were of the opinion that "an initial dose of 5 I.U. appears to be too high in association with a pathological pregnancy". A similar conclusion was made on the basis of clinical observations at the beginning of the present trial and 1 I.U. was selected as the initial dose.

It was generally not possible to let the patient herself administer the Partocon®. This means that the nursing staff had to help the patient 20 times. This may interfere with other work in a busy delivery room, although it may result in more effective observation of labour.

Syntocinon Buccal®

The results obtained with inductions by buccal tablets were good. The percentage of successful inductions reported by other workers varies from 64 to 89. The maximum total dosage administered has been as high as 4400 I.U. (Krzaniak, 1965). Uterine rupture has occurred, and Theobald (1965) among other authors has condemned the use of buccal tablets.

The highest total dosage (2600 I.U.) used in

Table XVIII *Birth weight*

Percentages in parentheses

Grams	P I.N.	S.B.	S.I.V	Total
< 1499	—	1 (0.8)	2 (1.2)	3 (0.7)[a]
1500– 499	—	*1 (0.8)*	*2 (1.2)*	*3 (0.7)*
2500–3499	44 (27)	36 (30)	65 (38)	145 (32)
3500–4499	110 (67)	75 (61)	96 (56)	281 (62)
≥ 4500	*11 (6.7)*	*8 (6.6)*	*5 (2.9)*	*24 (5.3)*
	165	121	170	456
(Twin pregnancy	—	—	11	11)

Foetuses died antenatally during 2nd trimester

Table XIX. *Signs of foetal distress without neonatal asphyxia*

Percentages in parentheses

	P I.N.	S.B	S.I.V	Total
Abnormal foetal heart rate[a]	1 (0 6)	5 (4 1)	10 (6.3)	16 (3 6)
Meconium in amniotic fluid	*15 (9 1)*	*8 (6.6)*	*11 (6 9)*	*34 (7 7)*
Abnormal foetal heart rate & meconium in amniotic fluid	1 (0.6)	2 (1 7)	3 (1 9)	6 (1 4)
	17 (10)	*15 (12)*	*24 (15)*	*56 (13)*

Heart rate ≥ 160/min or < 110/min or irregular

Case 1 A gravida III aged 33 whose previous deliveries had been *nine* and *10 years* earlier *Induction* had been performed on both occasions but the indication for it was not known. On this occasion labour was induced in the 41st week of gestation for toxaemia and suspected rupture of the membranes. The patient was given 2600 *LU of S.B. tablets without effect. A second induction,* likewise with 2600 LU of S.B. tablets, was performed in c 48 hours. Weak contractions were induced, but disappeared for almost 4 hours. Labour then started, the mother's blood pressure rose to 160 110. Foetal heart

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Percentages in parentheses
N B. 3 cases of antenatal foetal deaths not included

	P.I.N.	S.B	S.I.V	Total
Asphyxiated baby no signs of foetal distress noticed	4 (2.4)	4 (3.3)	5 (3 1)	13 (2.9)
Spontaneous delivery	2	4	3	9 (69)
Caesarean section	1	—	1	2 (15)
Breech delivery	1	—	1	2 (15)
Asphyxiated baby abnormal *foetal heart rate*	—	2 (1 7)	3 (1.9)	5 (1 1)
Spontaneous delivery	—	1	1	2 (40)
Caesarean section	—	1	1	2 (40)
Breech delivery	—	—	1	1 (20)
Asphyxiated baby meconium in amniotic fluid	—	1 (0.8)	1 (0 6)	(0.5)
Spontaneous delivery	—	1	1	2 (100)
Asphyxiated baby abnormal foetal heart rate, meconium in amniotic fluid	1 (0.6)	—	1 (0 6)	2 (0.5)
Vacuum extractor	1	—	—	1 (50)
Breech delivery	—	—	1	1 (50)
Intrapartum death (see Case Report)	—	1 (0 8)	—	1 (0 22)
Spontaneous delivery	—	1	—	1 (100)
Neonatal death (see Case Report)	1 (0 6)	—	1 (0.6)	(0 5)
Caesarean section	1	—	1	(100)
Asphyxia	5 (3 0)	7 (5.8)	10 (5 9)	2. (4 8)
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sounds ceased 75 min antepartum. The membranes did not rupture until the cervix was completely dilated; the amniotic fluid was green. The baby was stillborn, birth weight 3,540 g. The autopsy diagnosis was aspiration of amniotic fluid.

Case 2. A primigravida aged 26 had an induction performed in the 43rd week of gestation for postmaturity. She was given 764 I.U. of Partocon IN® solution. Labour started, but green amniotic fluid was observed at an early stage and Caesarean section was performed. The infant weighed 3,000 g, had an Apgar score of 3–7 and died at the age of 31 hours. The autopsy diagnosis was intrauterine neonatal pneumonia, aspiration of amniotic fluid, pulmonary hyaline membrane. The maternal listeria antibodies were elevated and, according to the pathologist, "infection towards the end of pregnancy" was involved.

Case 3. A gravida V aged 27 who had a history of threatened abortion in the sixth month of gestation during her third pregnancy. The previous pregnancies were otherwise normal. The membranes ruptured spontaneously in the 34th week of gestation. There was associated bleeding which appeared to be foetal according to Apt's test. Syntocinon® instillation was commenced; the patient received only 0.6 ml in all. There was more profuse bleeding after active labour started and Caesarean section was performed for suspected abruptio placentae. The baby's birth weight was 1,455 g, Apgar score 1–2, death ensued in 4 hours. Rupture of the marginal sinus was found in the placenta and the infant's autopsy diagnosis was pulmonary immaturity, incomplete pulmonary hyaline membrane, intra-alveolar and interstitial pulmonary haemorrhage, petechial haemorrhage of the epicardium, hemopericardium and immaturity.

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The highest total dosage (2600 I.U.) used b

this series was almost 1000 times the amount of intravenous oxytocin, and seems alarmingly great.

Good results (success percentage 80–81) have been obtained in recent years by some authors, e.g. *Chalmers et al (1966)* and *Wiese (1968)* by giving only 500–600 I U of buccal tablets. The incidence of excessive uterine activity was lower with this dosage than in a parallel group for which intravenous oxytocin was used

Thirty five patients of the S.B group had a history of complications in earlier deliveries. Seven of these patients had been delivered operatively four by Caesarean section, one by vacuum extraction and two by forceps. The corresponding group had two Caesarean sections and one vacuum extraction in the pregnancy studied.

Syntocinon Intravenous

The best results have been achieved in most investigations by intravenous oxytocin. That the percentage of successful inductions was lowest in this group of the present series can be attributed to the fact that this method of inducing labour was generally chosen in the cases where the maternal and especially the foetal condition was most critical, and when it was impossible to await a more favourable time for induction. This was true even in the years when either intranasal or buccal oxytocin was the principal method of induction. The treatment groups are thus not fully comparable (Table I) Primigravidas who required induction for toxaemia totalled 24 (15%) in the P I.N group 16 (13%) in the S.B. group and 43 (27%) in the S.I.V group. The outcome of induction could have been expected to be poorer in these cases than the average for all the groups. Yet this was true only of the S.I V group (induction was successful in 51%) the percentage of successful inductions was 71 in the P I.N and 75 in the S B. group

Great caution was exercised in intravenous administration for the basic reasons mentioned above. This caution is apparent from the fact that the average amount of oxytocin given in the S.I V group was the same independent of the final outcome in other words, no attempt was made to induce labour by increasing the dose The contrary view was taken by Turnbull & Anderson (1968) who increased the oxytocin concentration and the rate of flow at short intervals to a maximum of 337 mU min when 540 ml of 5 glucose solution contained 32 I.U of oxytocin and the infusion rate was 60 drops/min. They regarded their results as superior to those obtained by the conservative method, but there was at least one case of uterine rupture

Thirty-seven of the patients in the S.I V group had had complications in previous deliveries, and seven of them had been delivered operatively three Caesarean sections and four forceps or vacuum extractions. Two Caesarean sections were performed in this group in the present pregnancy

General

The average duration of hospital stay for the patients of the S.I V group was 15 7 days, for the S B. group 11 7 and the P I.N group 11 1 days. These figures reflect in some degree the results obtained by various methods, but they also reveal that the S.I.V group included the greatest number of critical cases requiring observation. Repeated failures waste hospital beds and increase the costs of treatment.

It must be admitted that for the present "no method of induction is both certain and safe and "that one should be as ready to defend the indications for induction as for Caesarean section" (Donald, 1964) In the author's opinion, however carefully planned and performed induction—irrespective of whether the oxytocin is administered intravenously intranasally or as buccal tablets—is often equally justified and at least as safe as Caesarean section when the object is delivery at a set time to forestall a risk to the mother and or the foetus. The necessary conditions are of course, that neither the maternal nor foetal state requires immediate termination of pregnancy and that delivery by the vaginal route is safe

Intravenous oxytocin confines the patient to her bed. An endeavour has been made to eliminate this drawback by means of buccal and intranasal preparation but they necessitate the administration of very big doses. Too little is still known about possible individual differences in their absorption from the mucosa. In addition, it is difficult to control how much is swallowed and thus destroyed by the patient for one reason or another The experience in this hospital was that the patients (and the staff) generally preferred the buccal form of administration to the intranasal method. Both of them have the disadvantage that

it is impossible to interrupt the absorption of oxytocin immediately when necessary

Thirteen (2.9%) infants of the series were born with asphyxia although no foetal distress was observed during labour The symptoms might perhaps have been observed in these cases, too, if they had been *followed more closely* The intensity of labour pains can be raised to a pathological level by the administration of oxytocin. Several *other risks* are associated with it in addition to *the danger of* foetal asphyxia, namely uterine rupture partial or complete detachment of the placenta, amniotic fluid embolism, prolapse of the cord, and a pathological uterine constriction ring. O'Sullivan (1965) had even to resort to general anaesthesia to relax uterine spasm when performing induction with Pitocin® buccal tablets. *In this series, too,* 11 patients (2.5%) had hypertonic contractions, but they were not accompanied by more serious complications.

Secondary hypotonic inertia was reported by Müller & Osler (1967), mostly in connection with intranasal administration. Donald (1964) also cautions against post-induction inertia, and there is probably reason to do so On the other hand, *it is possible that inertia of this kind points to a* primary abnormality of uterine function and induction, whatever the method employed, may not give good result in such cases as the inertia may continue "secondarily

The repeated f ilure of induction may upset the patient mentally and thus impair her cooperation during the rest of the delivery Careful consideration of the indications for induction, accurate evaluat on of the readiness of the uterus and the patient herself for induction, correct timing and close supervision during the procedure should be the aims, and the factors which may complicate the *procedure must alway be taken* into account.

REFERENCES

Blair R. G. Lancet *1* 637 1964
Bordin, N J Acta Obstet Gynec Scand *4)* 238 196..
Chalmers, J A & Moorhouse, H. M J Obstet Gynaec Brit Comm *73* 59 1966.
Donald, I Practical Obstetric Problems, Lloyd Luke Ltd London, 1964
Donaldson, M Proc Roy Soc Med *14* 19 1971
Fields, H Greene J W & Smith, K. Induction of Labour The Macmillan Co., New York 1965.
en Grut, I Fikes, T & Seeler, J C. Acta Obstet Gynec Scand 46 340 1967
Hellmann I et al. Amer J Obstet Gynec *14* 137 1927
Krammik, M. B J Irish Med Ass 56 113 1965
Maxwell, A. W J Obstet Gynaec Brit Comm *71* 37 1964
Müller, K. & Osler M Acta Obstet Gynec Scand, Suppl. 9 59 1967
Page, W W Proc Soc Exp Biol Med 52 195 1943.
O'Sullivan, J F.: Irish J Med Sci 470-67 1965
Theobald, G. W Brit Med *J 1* 190, 1965
Turnbull, A. C. & Anderson, A. B J Obstet Gynaec Brit Comm 75 32, 1968
Wiese, J Acta Obstet Gynec Scand 47 333 1968

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General

The average duration of hospital stay for the patients of the S I V group was 15 7 days, for the S B group 11 7 and the P I.N group 11 1 days. These figures reflect in some degree the results obtained by various methods, but they also reveal that the S I V group included the greatest number of critical cases requiring observation. Repeated failures waste hospital beds and increase the costs of treatment

It must be admitted that for the present "no method of induction is both certain and safe and "that one should be as ready to defend the indications for induction as for Caesarean section" (Donald, 1964) In the author's opinion, however carefully planned and performed induction—irrespective of whether the oxytocin is administered intravenously intranasally or as buccal tablets—is often equally justified and at least as safe as Caesarean section when the object is delivery at a set time to forestall a risk to the mother and/or the foetus. The necessary conditions are of course, that neither the maternal nor foetal state requires immediate termination of pregnancy and that delivery by the vaginal route is safe

Intravenous oxytocin confines the patient to her bed An endeavour has been made to eliminate this drawback by means of buccal and intranasal preparation, but they necessitate the administration of very big doses. Too little is still known about possible individual differences in their absorption from the mucosa In addition, it is difficult to control how much is swallowed and thus destroyed by the patient for one reason or another The experience in this hospital was that the patients (and the staff) generally preferred the buccal form of administration to the intranasal method Both of them have the disadvantage that

it is impossible to interrupt the absorption of oxytocin immediately when necessary

Thirteen (2.9%) infants of the series were born with asphyxia although no foetal distress was observed during labour. The symptoms might perhaps have been observed in these cases, too, if they had been followed more closely. The intensity of labour pains can be raised to a pathological level by the administration of oxytocin. Several other risks are associated with it in addition to the danger of foetal asphyxia, namely uterine rupture, partial or complete detachment of the placenta, amniotic fluid embolism, prolapse of the cord, and a pathological uterine constriction ring. O'Sullivan (1965) had even to resort to general anaesthesia to relax uterine spasm when performing induction with Pitocin® buccal tablets. In this series, too, 11 patients (2.5%) had hyper tonic contractions, but they were not accompanied by more serious complications.

Secondary hypotonic inertia was reported by Muller & Osler (1967) mostly in connection with intranasal administration. Donald (1964) also cautions against post-induction inertia, and there is probably reason to do so. On the other hand, it is possible that inertia of this kind points to a primary abnormality of uterine function and induction, whatever the method employed, may not give a good result in such cases as the inertia may continue "secondarily".

The repeated failure of induction may upset the patient mentally and thus impair her cooperation during the est of the delivery. Careful consideration of the indications for induction, accurate evaluation of the readiness of the uterus and the patient herself for induction, correct timing and close supervision during the procedure should be the aim, and the factors which may complicate the procedure must always be taken into account.

REFERENCES

Blair, R. G. Lancet *1* 637 1964.

Borglin, N. E. Acta Obstet Gynec Scand *41* 238 1962.

Chalmers, J. A. & Moorhouse, H. M. J Obstet Gynaec Brit Comm *73* 99 1966.

Donald, I. Practical Obstetric Problems. Lloyd Luke Ltd., London, 1964.

Donaldson, M. Proc Roy Soc Med *14* 19 1921.

Ellis, H. Greene, J. W. & Smith, K.: Induction of Labour. The Macmillan Co., New York, 1965.

van Gent, I. Tuber, T. & Seiden, J. C. Acta Obstet Gyne Scand *46* 340 1967.

Hofbauer, J. et al. Amer J Obstet Gynec *14* 137 1927.

Kremelak, M. B. J Irish Med Ass *56* 113 1965.

Maxwell, A. W. J Obstet Gynaec Brit Comm *71* 37 1964.

Muller, K. & Osler, M. Acta Obstet Gynec Scand, Suppl. *9* 99 1967.

Page, W. W. Proc Soc Exp Biol Med *5* 195 1943.

O'Sullivan, J. F. Irish J Med Sci *470* 67 1965.

Theobald, G. W. Brit Med J *1* 190, 1965.

Turnbull, A. C. & Anderson, A. B. J Obstet Gynaec Brit Comm *75* 32, 1968.

Wase, J. Acta Obstet Gynec Scand *47* 333 1968.

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this series was almost 1000 times the amount of intravenous oxytocin, and seems alarmingly great.

Good results (success percentage 80–81) have been obtained in recent years by some authors e.g. Chalmers et al (1966) and Wiese (1968) by giving only 500–600 I U of buccal tablets. The incidence of excessive uterine activity was lower with this dosage than in a parallel group for which intravenous oxytocin was used.

Thirty-five patients of the S B group had a history of complications in earlier deliveries. Seven of these patients had been delivered operatively: four by Caesarean section, one by vacuum extraction and two by forceps. The corresponding group had two Caesarean sections and one vacuum extraction in the pregnancy studied

Syntocinon Intravenous

The best results have been achieved in most investigations by intravenous oxytocin. That the percentage of successful inductions was lowest in this group of the present series can be attributed to the fact that this method of inducing labour was generally chosen in the cases where the maternal and especially the foetal condition was most critical and when it was impossible to await a more favourable time for induction. This was true even in the years when either intranasal or buccal oxytocin was the principal method of induction. The treatment groups are thus not fully comparable (Table I) Primigravidas who required induction for toxaemia totalled 24 (15%) in the P I N group, 16 (13%) in the S.B group and 43 (27%) in the S.I.V group The outcome of induction could have been expected to be poorer in these cases than the average for all the groups. Yet this was true only of the S.I V group (induction was successful in 51%) the percentage of successful inductions was 71 in the P I.N and 75 in the S B group

Great caution was exercised in intravenous administration for the basic reasons mentioned above This caution is apparent from the fact that the average amount of oxytocin given in the S.I.V group was the same independent of the final outcome in other words, no attempt was made to induce labour by increasing the dose The contrary view was taken by Turnbull & Anderson (1968) who increased the oxytocin concentration and the rate of flow at short intervals to a maximum of 337 mU/min when 540 ml of 5 glucose solution contained 32 I U of oxytocin and the infusion rate was 60 drops/min. They regarded their results as superior to those obtained by the conservative method, but there was at least one case of uterine rupture

Thirty-seven of the patients in the S.I.V group had had complications in previous deliveries, and seven of them had been delivered operatively three Caesarean sections and four forceps or vacuum extractions. Two Caesarean sections were performed in this group in the present pregnancy

General

The average duration of hospital stay for the patients of the S.I V group was 15 7 days, for the S B group 11 7 and the P I N group 11 1 days. These figures reflect in some degree the results obtained by various methods, but they also reveal that the S.I V group included the greatest number of critical cases requiring observation. Repeated failures waste hospital beds and increase the costs of treatment.

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THE QUANTITATIVE ESTIMATION OF FOETAL ERYTHROCYTES IN MATERNAL BLOOD

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Abstract. The number of foetal erythrocytes in maternal blood is determined by adding yeast cells to the sample before preparation of the smear, extraction and staining. 25–1100 foetal erythrocytes per µl blood, corresponding to a foeto-maternal transfusion of about 20–900 µl are recovered with an average coefficient of variation of 20%. The clinical application of the method is demonstrated by following the rate of disappearance of the foetal erythrocytes from the maternal blood after foeto-maternal transfusion.

The increasing interest in the problems of immunisation of pregnant women by foeto-maternal transfusions, and especially in the possibility of rhesus prophylaxis by treating exposed women with anti-D-globulin, makes a rapid and simple routine method of estimating small amounts of foetal erythrocytes (F.E.) in the maternal blood desirable.

Kleihauer et al. (1957, 1960) described a qualitative method by which F.E. can be distinguished from maternal erythrocytes, the principle of the method being the extraction of adult haemoglobin (HbA) from the erythrocytes in a smear from which the foetal haemoglobin (HbF) had not been extracted. The Kleihauer-positive cells can be found easily in the smear while the decolourized maternal cells can hardly be distinguished or are invisible.

The Kleihauer method detects smaller admixture of foetal blood than does the assay of alkaline resistant haemoglobin (Kristoffersen, 1967) and immunochemical assay of HbF (Schneider et al. 1963). Therefore several authors have tried to improve the method for quantitative estimation of F.E. For instance, Zipursky et al. (1963) and Finn et al. (1961) counted F.E. during certain periods and compared the counts with recovery experiments, a method which seems hardly reproducible in different laboratories. Schneider et al. (1963) and Lorber et al. (1965) developed a technique of counting which produced considerably more exact results. By the use of cover slips and microscope eye-piece with divided squares of known size both foetal and maternal cells were counted. By recovery experiments these authors showed that the admixture of 50 µl foetal blood to 5 l of donor blood could be estimated quantitatively with a maximal coefficient of variation of 35%.

AUTHOR'S INVESTIGATIONS

Principle

A known number of particles of the same size as erythrocytes was added to a measured amount of maternal blood. After staining according to Kleihauer F.E. were counted with the test particles as reference.

Method

Yeast cells were used as test particles. Baking yeast ("Malthes, Cross" yeast, Saccharomyces cerevisiae, Danish Fermentation Industry, Copenhagen, Race no. 102) was fractioned by suspension.

About 5 g yeast cells were suspended in 200 ml diluting agent (NaCl 6.55 g, 1/15 M KH_2PO_4 9.00 ml, 1/15 M Na_2HPO_4 36.00 ml, 35–40% Formaldehyde solution 5.00 ml, H_2O 950 ml) in a cylindrical glass (200 × 35 mm) and placed at 4°C for 30 min. The cloudy solution above

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Table I *Results of recovery experiments with foetal erythrocytes in compatible donor blood*

Six series of dilutions are recorded. Units: F.E. per µl. b: double counts of six blood samples, c: mean values of double counts, d: expected values

Dilution Series of dilutions no.	1/1 b	1/1 c	1/1 d	1/2 b	1/2 c	1/2 d	1/4 b	1/4 c	1/4 d	1/8 b	1/8 c	1/8 d	1/16 b	1/16 c	1/16 d
1	373 290	337	392	217 282	250	196	140 128	134	98	73 51	62	49	64 45	55	24
2	487 557	522	474	259 253	256	237	116 125	120	118	72 90	81	59	35 10	23	30
3	425 457	441	413	237 168	202	207	102 112	107	104	46 106	76	51	46 20	33	25
4	593 840	717	706	371 376	374	353	170 214	192	177	99 73	86	88	41 40	41	44
5	1130 996	1063	1099	383 571	477	549	323 311	317	274	122 140	131	137	80 84	82	68
6	840 780	810	839	430 311	370	420	189 215	202	209	145 153	149	105	31 67	49	52
s^2	9493 97	(15)		4879 70	(22)		257 16	(9)		452 21	(21%)		248 16	(34)	

Recovery periments

A known amount of compatible blood from new born infants was added to donor blood not containing any Kleihauer-positive cells, the concentration of F.E. thus produced was about 500–1000 per µl blood. A sample of this mixed blood as diluted with an equal volume of donor blood, and three further 50 50 dilutions with donor blood were carried out. Thus 1/1 1/2, 1 4 1/8 and 1 16 mixtures of foetal and donor blood were produced. This procedure was performed in duplicate. The results of six double dilution series obtained by the technique mentioned above are shown in Fig and Table I.

The evaluation of the count error was based on th usual formula involving a series of double determinations: $= d^2/2n$ n being the number of the double determinations, and d the difference between the two counts in each blood sample. It appears that the accuracy of the count varies with the dilution, the variances in 1/1 and 1/2 were significantly higher than in 1/4. Because of this it is not possible to indicate a count accuracy for the entire rang of readings. A comparison between the observed mean values and the expected values did not show significant differences in any part of the experiment. (Method of paired comparisons.)

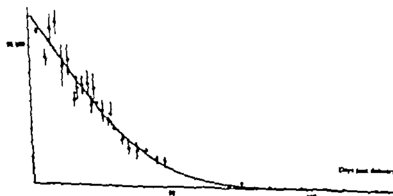


Fig. 3 The disappearance of foetal erythrocytes from the maternal circulation recording mean and range of each determination.

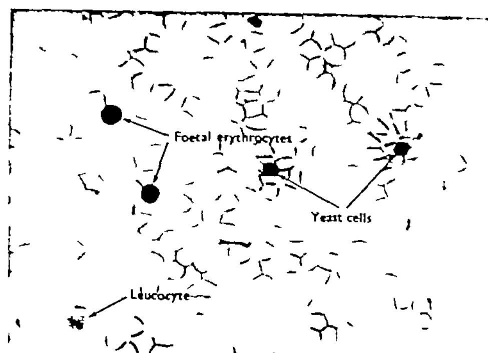


Fig. 1 T o foetal erythrocytes and tw yeast cells surrounded by maternal erythrocytes in a stained smear

the sediment was decanted into a glass of equal size and left at 4°C for ?0– 4 hours. The remaining cloudy liquid was aspirated from the sediment. The sediment was now suspended by adding ?00 ml pure diluting agent, shaken and left for a further ?0– 4 hours at 4°C The cloudy liquid was again aspirated from the sediment. A yeast cell suspension was produced from the sediment containing about 10 000 cells per μl. The exact number was found by microscopy or electronic counting. (Celloscope: Aperture Current 9? Threshold 40). At 4°C a reasonably constant count of the suspension was found for at least 14 days.

25 μl of yeast cell suspension and 1000 μl of heparinstabilised venous blood were transferred by pipette into a test tube (80 × 10 mm) containing a glass ball. After thorough mixing a thin smear was made and treated according to Kleihauer et al (1960).

After 10–60 min drying in air it was fixed with 80% ethanol for 5 min, rinsed with distilled water and dried in air. Extraction with sodium-phosphate-citric acid buffer (0._ M Na_2HPO_4 47 ml, 0.1 M $C_6H_8O_7$ 7 3 ml, pH adjusted to 3._ 3.3) at 37 C lasted 4 min. Thereafter the smear was rinsed with abundant water and stained for 3 min with Ehrlich's acid Hematoxylin, rinsed again and stained for 3 min with 0.1 erythrosin. Finally it was rinsed with distilled water and dried in air.

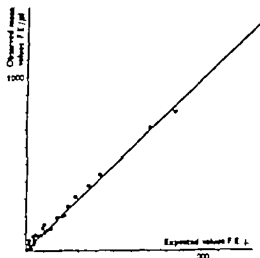


Fig. The results of recovery experiments correlated with the expected number

Microscopy

Foetal erythrocytes (homogenous, red) and yeast cells (purple refracting) (Fig. 1) were counted in the same squares which were randomly chosen in the direction in which the smear was made and along the whole length of the smear. At least _5 yeast cells should be counted.

Calculation

The concentration of F.E. in the blood sample =

$$\frac{a \cdot 25 \cdot F}{1000 \cdot Y} \text{ cells per } \mu l.$$

a – the concentration of the yeast cell suspension (cells/μl)

F the recorded number of foetal erythrocytes.

Y the recorded number of yeast cells.

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Six series of dilutions are recorded. Units: F.E. per µl, *b* double counts of six blood samples; *c* mean values of double counts *d* expected values

Dilution Series of dilutions no.	1/1 *b*		*d*	1/2 *b*		*d*	1/4 *b*		*d*	1/8 *b*		*d*	1/16 *b*		*d*
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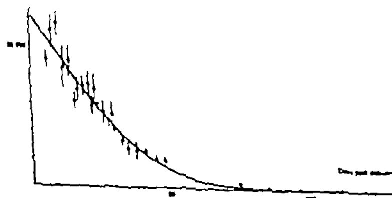


Fig. 3. The disappearance of foetal erythrocytes from the maternal circulation recording mean and range of each determination.

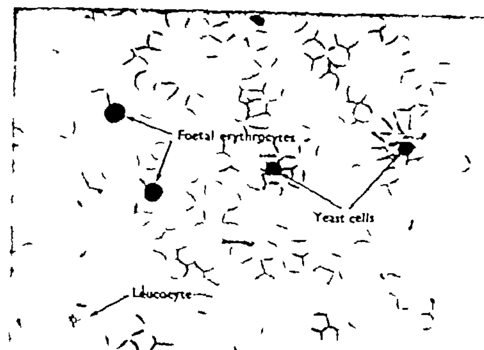


Fig. 1. Two foetal erythrocytes and two yeast cells surrounded by maternal erythrocytes in stained smear.

the sediment was decanted into a glass of equal size and left at 4°C for 20–24 hours. The remaining cloudy liquid was aspirated from the sediment. The sediment was now suspended by adding 200 ml pure diluting agent, shaken and left for a further 20–24 hours at 4°C. The cloudy liquid was again aspirated from the sediment. A yeast cell suspension was produced from the sediment containing about 10,000 cells per µl. The exact number was found by microscopy or electronic counting. (Celloscope: Aperture Current 95, Threshold 40). At 4°C a reasonably constant count of the suspension was found for at least 14 days.

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After 10–60 min drying in air it was fixed with 80 % ethanol for 5 min, rinsed with distilled water and dried in air. Extraction with sodium-phosphate-citric acid buffer (0.2 M Na_2HPO_4 47 ml, 0.1 M $C_6H_8O_7$ 53 ml, pH adjusted to 3.2–3.3) at 37°C lasted 4 min. Thereafter the smear was rinsed with abundant water and stained for 3 min with Ehrlich's acid Hematoxylin, rinsed again and stained for 3 min with 0.1% erythrosin. Finally it was rinsed with distilled water and dried in air.

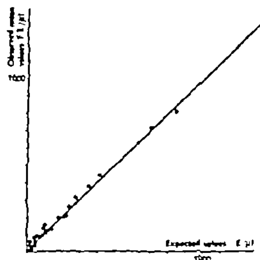


Fig. The result of recovery experiments correlated with the expected number.

Microscopy

Foetal erythrocytes (homogenous, red) and yeast cells (purple, refracting) (Fig. 1) were counted in the same squares which were randomly chosen in the direction in which the smear was made and along the whole length of the smear. At least 25 yeast cells should be counted.

Calculation

The concentration of F.E. in the blood sample =

$$\frac{a \cdot 25 \cdot F}{1000 \cdot Y} \text{ cells per } \mu l.$$

a = the concentration of the yeast cell suspension (cells/µl)

F = the recorded number of foetal erythrocytes.

Y = the recorded number of yeast cells

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A SIMPLE AND RAPID CLINICAL METHOD FOR THE SERIAL ESTIMATION OF OESTRIOL IN PREGNANCY URINE

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Abstract. A simple and rapid clinical routine method is described for the serial estimation of oestriol in pregnancy urine. It involves enzyme hydrolysis at an elevated temperature, ether extraction, solvent partition and colorimetric estimation by means of a modified Kober reaction. The method fulfils the established criteria of reliability when applied to pregnancy urine specimens containing 2.0 µg oestriol per ml, or more. The procedure is so simple and rapid that the average technician can complete the analysis of 24 specimens within 5 hours.

Since the publication of the basic principles of oestrogen assays in the form of Kober chromogens (Bauld, 1954, 1955, 1956; Brown, 1955), a great number of modified methods have been described for the clinical routine estimation of oestriol (e.g. Hobkirk et al., 1960; Taylor et al., 1961; Furuhjelm, 1962; Klopper & Wilson, 1962; Brown & Coyle, 1963; Beling, 1963; Frandsen, 1963; and Green et al., 1965; Dale et al., 1965; the literature published prior to 1960 has been reviewed by Diczfalusy & Lauritzen, 1961). Most of the published methods are, however, either laborious and time-consuming, or of small specificity. Urinary oestriol assays are of great value to the clinician in monitoring the condition of the intrauterine patient; however, the value of such assays is considerably diminished if the results of such assays are not available to the clinician within a few hours and if the patients cannot be followed by serial (preferably daily) oestriol assays.

In this communication a method is proposed, which yields reliable estimates of oestriol in pregnancy urine specimens containing at least 2.0 µg of oestriol/ml. The method which has been evolved from that described by Beling (1963) is so simple and rapid that the average technician can complete the analysis of 24 urine samples within 5 hours.

MATERIAL

Trivial names. The following trivial names are used throughout this paper: *oestriol*: 1,3,5(10)-oestratriene-3,16α,17β-triol; *6α-hydroxy-oestriol*: 1,3,5(10)-oestratriene-3,6α,16α,17β-tetrol; *15α-hydroxy-oestriol*: 1,3,5(10)-oestratriene-3,15α,16α,17β-tetrol; *oestriol-3-sulphate*: 16α,17β-dihydroxy-1,3,5(10)-oestratrien-3-yl-sulphate; *oestriol-3-glucosiduronate*: 16α,17β-dihydroxy-1,3,5(10)-oestratrien-3-yl-β-D-glucopyranosiduronate; *oestriol-16-glucosiduronate*: 3,17β-dihydroxy-1,3,5(10)-oestratrien-16α-yl-β-D-glucopyranosiduronate; *oestriol-3-sulphate, 16-glucosiduronate*: 17β-hydroxy-oestra-1,3,5(10)-trien-3-yl-sulphate, 16α-yl-β-D-glucopyranosiduronate.

Reagents. All solvents were of analytical grade and were redistilled before use. Ethyl ether (Mallinckrodt) was peroxide-free and was freshly distilled before use. The *Helix pomatia* enzyme preparation was purchased from Industrie Biologique Française, Gennevilliers, France. It contained 100 000 Fishman units of β-glucuronidase and [illegible]00 000 Roy units of sulphatase per ml. The sulphuric acid reagent for oestriol was prepared according to the specifications of Nocke (1961) and contained 2% (w/v) of quinol (E. Merck, Darmstadt) in 76% (v/v) aqueous sulphuric acid (E. Merck, Darmstadt). Oestriol-16-^{14}C 16-glucosiduronate was biosynthesized according to the method of [illegible] et al. (1964) and oestriol-15-^{3}H 3-glucosiduronate according to the method of Goebelsmann et al. (196[illegible]). Oestriol-16-glucosiduronate was a gift from Professor W. M. Allen, St Louis, Mo., USA.

The proposed method

Enzyme hydrolysis. An aliquot of 0.5 ml of filtered urine, from a carefully mixed 24-hour specimen is pipetted into a glass-stoppered tube (150 × 22 mm). Generally 24 such samples are processed simultaneously in a common wooden frame. Following the addition of 5.5 ml of distilled water 0.7 ml of an 1.5 M acetate buffer (pH

For illustration of the clinical application of the method the recorded results of a major foeto-maternal transfusion and of the disappearance of the foetal erythrocytes are shown in Fig 3

A female patient, aged 22, blood group O Rh D positive and in her 31st week of pregnancy was involved in a traffic accident, as a result of which she suffered abdominal trauma leading to vaginal bleeding. Nine days later she gave birth to a live female child, birth-weight 1350 g, length 40 cm, haemoglobin 9 0 g% blood group O Rh D positive Two days after delivery about 55 000 F.E. per μl maternal blood were found, which is about 1 4 % of the total number of erythrocytes. Repeated tests were made on the maternal blood until no foetal erythrocytes could be demonstrated 125 days after delivery

DISCUSSION

In addition to experiments with baking yeast cells, experiments have been performed with maize starch talcum powder human erythrocytes (Erythro-trol®) and killed beer yeast cells as test particles. Staining of the test particles was tried before mixing with the blood sample as well as after the preparation of the smear The best results were obtained with baking yeast cells which were clearly stained without the use of new staining methods These cells were evenly dispersed in the smear but like the leucocytes, they are inclined to be concentrated at the edge of the smear This is of no special importance when the counting is performed only in successive fields in the direction in which the smear was made and along the whole length of the smear

By counting 25 yeast cells an area of about 0 1 μl blood is examined Time for counting was about 15–20 min Theoretically the accuracy of the result can be increased by examination of larger areas. The accuracy of the method should be expected to increase when reference particles are found dispersed in the smear like the Kleihauer positive cells.

When counting F E. after a major foeto-maternal transfusion a higher concentration of yeast cells is preferable in order to obtain an approximately equal number of F E. and test cells. Accordingly the amount of blood examined will be less than 0 1 μl

A survival time of F E in the maternal circulation of a minimum of 111 days, as shown in Fig 3 was in accordance with the results of Kleihauer (1966) who found an average survival time of 70–80 days and in some women, foetal erythrocytes even 120–130 days after delivery

ACKNOWLEDGEMENT

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REFERENCES

Finn, R., Clarke C. A., Donohoe, W T McConnell *R. B., Sheppard, P M Lehane D & Kulke W* Brit Med J *1* 1486 1961

Kleihauer E., Braun, H. & Betke K., Klin Wschr 35 637 1957

Kleihauer E. & Betke, K., Internist (Berl) *1* 292 1960

Kleihauer E., Fetales Hämoglobin und fetale Erythrozyten. Stuttgart, 1966.

Kristoffersen, K., Danish Med Bull *14* 176 1967

Lorbeer H. & Schneider J Ärztl Lab *11* 313 1965

Schneider J & Ludwig, G A., Klin Wschr *41* 563 1963

Zipursky A., Pollock, J Neelands, P Chown, B. & Israels, L. G Lancet 489 1963

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Table III. *Estimates of precision expressed as the estimates of standard deviation (S.D.) of results from their means (from duplicate determination)*

Range (mg/24 h)	No. of patients	No. of duplicates	Average (mg/24 h)	S.D.
0–5	9	23	2.3	0.23
5–10	3	15	7.7	0.22
10–20	11	44	15.7	0.71
20–30	8	44	29.5	1.14

uate are excreted (Beling, 1963; Goebelsmann et al., 1965 *a* and *b*, 1966, 1968). Although—as shown in Table IV—in the present study the completeness of enzyme hydrolysis was only investigated following the addition of the 3- and 16-monoglucosiduronates, the conditions of enzymic hydrolysis adopted in this investigation are such, that they should result in a complete hydrolysis of oestriol-3-sulphate (e.g. Diczfalusy et al., 1964) as well as of that of oestriol-3-sulphate 16-glucosiduronate (Troen et al., 1961).

A rapid method for oestriol in pregnancy urine must yield clean extracts in a reasonably short time. Therefore, following a suggestion of Dr R. Hähnel we have studied the conditions of short enzyme hydrolysis at elevated temperature. As indicated in Table I, fifteen pregnancy urine specimens from various patients were hydrolyzed for 30 min at 55 C with 0.1 ml of concentrated enzyme solution and for 2 × 30 min with the double amount of enzyme and the yields were compared with those obtained following 16 hours of enzymic hydrolysis at 37 according to the specifications of Beling (1963).

It appears from the data of Table I, that the conditions adopted in our method will liberate 87 ± 7.6 of the amount of conjugated oestriol hydrolyzed by the usual enzymic method over night. This is considered to be a satisfactory yield, for an assay method in which speed is of utmost importance.

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Colour development and colorimetry. The use of the sulphuric acid reagent of Nocke (1961) instead of that described by Brown (1955) greatly enhances the sensitivity of the Kober reaction for oestriol (e.g. Adlercreutz, 196_). The experimental verification of the assumption underlying the use of the colour correction equation of Allen (1950) when applied to the Kober chromogens formed from urinary oestriol fractions has been presented in a previous communication (Diczfalusy, 1955). Finally, although the oestriol fraction obtained in the present method may contain smaller amounts of polar oestrogens, the quantities of these in relation to that of oestriol are negligible (e.g. Breuer 1964; Lisboa et al., 1967; Diczfalusy & Mancuso, 1969). In addition, the Kober chromogenicity of these polar oestrogens, such as 6α-hydroxy-oestriol and 15α-hydroxy-oestriol is much less than that of oestriol (e.g. Diczfalusy & Lauritzen, 1961; Zucconi et al., 1967).

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Standard added	Amount	No. of duplicate determinations	Average recovery (%)	S.D.
Oestriol-16-14C-16-glucosiduronate	360 DPM	6	95	11.2
Oestriol-2,4-3H-16-glucosiduronate	12 000 DPM	20	95	371.0
Oestriol-3-glucosiduronate	2 µg	10	90	0.06
Oestriol-16-glucosiduronate	8 µg	10	80	0.10

1 [illegible]

Table I *Influence of the conditions of enzymic hydrolysis on the yield of oestriol*

Urine sample	Volume (ml)	Yield of oestriol (mg) by methods A	B[b]	C[c]
1	1 000	10.5	15 1	16.2
2	905	10.5	12.9	18.2
3	1 920	49.3	60.1	70 8
4	1 700	61 7	75.3	87 4
5	1 375	58.4	73.6	80.0
6	880	32.6	45.2	51 7
7	820	2.7	3.2	3.2
8	800	2.6	3 0	3.5
9	1 325	5.8	6.1	7 0
10	1 170	5 4	5 6	6.9
11	1 150	27.9	41 4	44.3
12	1 650	23 4	3[illegible]3	33.3
13	7[illegible]0	12.6	18 9	20.5
14	975	11 9	19.3	24 4
15	1 075	4.9	5.9	7 4
Total		3[illegible]0.2	417 9	474.8

10 000 U of β-glucuronidase and 80 000 U of sulphatase t 55 for 30 min.
[b] 10 000 U of β-glucuronidase and 2 80 000 U of sulphatase at 55 for 2 30 min.
1 200 U of β-glucuronidase and 9 600 U of sulphatase at 37 C for 16 hours.

4 1) and 0 1 ml of the undiluted enzyme preparation (corresponding to 10 000 U of β-glucuronidase and 80 000 U of sulphatase) the sample is incubated at 55 for 30 min. At this stage an additional 0 1 ml of the concentrated enzyme solution is added and incubation at 55 is continued for another 30 min.

Extraction After cooling in ice water 2.5 ml of a saturated carbonate buffer of pH 10.5 (Brown, 1955) are added to the hydrolyzed urine and oestriol is extracted with 10 ml of ethyl ether Twenty four samples are extracted simultaneously in a frame by hand, or by the use of a shaking apparatus (e g Vestergaard 1951) Following the separation of the organic and aqueous phases, the ether is transferred to another ("clean") tube by means of a syringe–pipette The ether is carefully evaporated in a water bath at 36–40 The urine specimens are extracted with another aliquot of 10 ml of ether the ether transferred to the clean tub and evaporated to dryness. Five ml of a benzene-petroleum ether mixture (1 1 v/v) are then pipetted into the dry tubes followed by the addition of 5 0 ml distilled water The tubes are thoroughly shaken for a minute or two After the complete separation of the two layers, the upper layer (organic phase) is removed by suction and discarded. The remaining aqueous phase is extracted twice with 10 ml of ether as above, the ether extracts are combined and evaporated to dryness.

Colour development and colorimetry To each of 27 tubes (including 24 urine samples, one water blank and two concentrations of authentic oestriol) 2.1 ml of sulphuric acid reagent (Nocke, 1961) are added and the rack of tubes is heated in a vigorously boiling water bath for exactly 20 min. In order to ensure proper mixing, the samples must be shaken a couple of times during the first 5 min of boiling. Following careful cooling, 1.1 ml of distilled water is added to each tube by gentle shaking and the tubes are heated for a second time in a boiling water bath for 14 min. Following cooling (ice-water) the optical density is measured in a spectrophotometer at wavelengths 464 510 and 556 mμ and the corrected optical density is calculated according to the formula of Allen (1950) as modified by Brown (1955).

Comments on the proposed method

Enzyme hydrolysis. More than 96% of the oestriol of pregnancy urine is present in the form of oestriol 16-glucosiduronate and oestriol-3-glucosiduronate, and only negligible amounts of oestriol-3-sulphate and oestriol 3-sulphate 16-glucosiduro-

Table II *Yield of oestriol (mg/24 h) in four subsequent 24 hours collections obtained from 17 patients, using the method of Beling (1963) and the present method, respectively*

Patient	Method of Beling (1963)				Present method			
L. G	0.5	0 6	0 6	0 7	[illegible]7	0 8	2.3	1 4
A B	1 6	1 0	1 4	1.3	2.9	2 0	1 8	[illegible]
B. G	1 5	4 6	5 4	5 3	7 4	9 1	5 0	6 5
J E	7 6	9 3	4 1	10.4	8.[illegible]	9.8	9 8	10 5
L. S	9 0	1 3	9 3	6.5	8.5	11.5	1 4	10 8
W M	5 4	7 9	10 8	8 0	13.5	15 0	14	14 2
B N	18 4	15 6	13 0	21 2	15 6	16 6	[illegible]0 0	19 7
R. M	7 2	10.[illegible]	14 4	11 3	24 5	14 0	18 2	19
W P	17 3	14.0	19 7	17 0	19 1	23.9	30 0	43
G G	1 3	5 3	[illegible]3 6	21 2	[illegible]7 7	29 7	[illegible]8 6	23 5
A G	26.6	26 6	27 4	[illegible]6 9	30 8	36 4	4[illegible]7	36 6
J A.	1 6	4 6	8 8	14 9	20 5	26 6	[illegible]5 8	25 0
J G	25 3	27 9	16 9	23 4	37 8	39 5	45 0	40 8
A. S	15 2	9 6	17 8	13 3	19 0	23.3	20.3	20 1
N S.	27 9	34 0	30 8	15.[illegible]	37.3	49.3	45 7	47 7
A. J	14 4	4 8	18.2	14 4	14.9	18 8	19 0	17 1
G A.	3 6	7.8	10 1	9 6	9 1	12 8	9 8	8 4

Table III. *Estimates of precision expressed as the estimates of standard deviation (S.D.) of results from their means (from duplicate determination)*

Range (mg/24 h)	No of patients	No. of duplicates	Average (mg/24 h)	S D
0–5	9	23	2.3	0.23
5–10	3	19	7.7	0.22
10–20	11	46	15.7	0.71
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13	770	1 6	18.9	70.5
14	975	11.9	19.3	24 4
15	1 075	4.9	5.9	7 4
Total		320.2	417.9	474 8

10 000 U of β-glucuronidase and 80 000 U of sulphatase at 55 for 30 min.
[b] 2 10 000 U of β-glucuronidase and 2 80 000 U of sulphatase at 55 to 2 30 min.
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Patient	Method of Beling (1963)				Present method			
L. G	0.5	0 6	0 6	0 7	2 7	0 8	2 3	1 4
A. B.	1 6	1 0	1 4	1 1	9	0	1 8	2 2
B. G	1 5	4 6	5 4	5 1	7 4	9 1	5 0	6 5
J E.	7 6	9 3	4 1	10 4	8	9 8	9 8	10 5
L. S.	9 0	3 3	9 3	6 5	8 5	11 5	1 4	10 8
W M	5 4	7 9	10 8	8 0	11 5	15 0	14	14
B. N.	18 4	15 6	13 0	1	13 6	16 6	20 0	19 7
R. M	7 2	10 2	14 4	11 3	4 5	14 0	18 2	1 9
W P	17 3	14 0	19 7	17 0	19 1	1 9	30 0	4 3
G G	1 1	5 3	3 6	21 2	7 7	9 7	8 6	8 3
A. G	6 6	26 8	27 4	9	30 8	16 4	4 7	34 6
J A.	21 6	4 6	8 8	14 9	0 5	6 6	5 8	25 0
J G	5 3	7 9	16 9	3 4	37 8	19 5	45 0	40 8
A. S.	15 2	9 6	17 8	11 3	19 0	3 1	0 1	0 3
N S.	27 9	34 0	30.8	15.2	37 3	49 1	45 7	47 7
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Another approach to the assessment of the specificity of the method consists of the study of the spectral characteristics of the Kober chromogens formed. In Fig. 2 the absorbance of the Kober chromogen formed from a late pregnancy urine specimen is compared with that of authentic oestriol.

It appears from the data of Fig. 2 that the purity of the Kober chromogen formed from the crude extract of late pregnancy urine compares most favourably with that of extensively purified oestriol methyl ether fractions obtained by classical methods, such as that of Brown et al. (1957).

In Fig. 3 the spectral characteristics of the Kober chromogens obtained by the proposed method from mid-gestation samples are presented.

It can be seen, that even in an extract containing only 4.3 μg of oestriol, there was a well marked peak corresponding to the absorption maximum of the Kober colour formed. It appears therefore, that the specificity of the proposed method is fairly satisfactory.

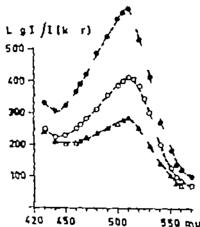


Fig. 3 Absorption spectra of the Kober chromogens prepared by the present method from pregnancy urine specimens from three normally pregnant women (mid-gestation). The three samples contained 13.2 (filled circles), 8.6 (open circles) and 4.3 (open triangles) micrograms of oestriol, respectively.

DISCUSSION

The dilemma inherent in the development of a clinically useful rapid and simple method for the assay of oestriol in pregnancy urine is to reach a sensible compromise between speed and reliability. In order to provide information of practical value, it is essential that assay results should be available within few hours. However it is equally important that the method should fulfil the recognized criteria of reliability as far as precision, accuracy, sensitivity and last but not least specificity is concerned. The crucial point appears to be the problem of hydrolysis of the oestriol conjugates. Enzymic methods yield relatively clean extracts, but are time-consuming, whereas hot acid hydrolysis necessitates only a short time for completion, but yields highly pigmented extracts, requiring most extensive purification. Thus much could be gained by the development of a rapid method of enzymic hydrolysis.

For the purpose of routine determination of oestriol, the assay method developed by Beling (1963) was used by us during the past few years. The present method has been evolved from that described by Beling ((1963); indeed, several useful steps of his method are incorporated in the present technique. However the method of Beling (1963) has two major disadvantages. It is time-consuming because of the gel-filtration and overnight enzymic hydrolysis involved and it does not measure oestriol 3-glucosiduronate only oestriol 16-glucosiduronate. It is established, that at mid-gestation, oestriol-3-glucosiduronate constitutes some 30–40% of the total oestriol content of pregnancy urine (Beling, 1963 Goebelsmann et al., 1966).

The present method utilizes a short enzymic hydrolysis (60 min) at an elevated temperature and consists only of a few subsequent partition steps. Nevertheless, the method seems to fulfil the established criteria of reliability when applied to pregnancy urine specimens containing 2.0 μg oestriol/ml, or more. Furthermore, the method is so simple and rapid that the average technician can complete the analysis of 24 specimens within 5 hours. Although the method is described for the analysis of 24-hour urine specimens, preliminary evidence indicates that collection of 24 hour specimens may not be required, provided the oestriol content of the urine is related to the concentration of endogenous creatinine. Using such an approach, it seems possible to monitor the condition of the foetus by oestriol assay conducted with a minimal delay.

In the present communication no normal values are presented, since it is felt that more weight should be given to the day to day trend of oestriol

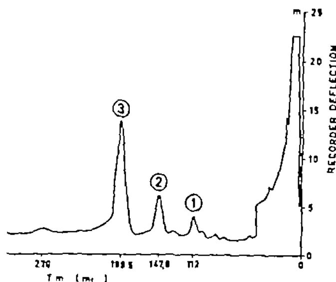


Fig 1 Gas liquid chromatography on methylsilicone (SE 30) of the trimethyl silyl ethers formed from the extract of a pregnancy urine sample. Conditions 2.0% SE 30 argon inlet pressure 1.5 kg/cm² column temperature 1?°C flash heater and detector (hydrogen flame) 45°C. Peaks no. 1 and 2 represent unidentified compounds, peak no. 3 is oestriol.

repeatedly the time required for the completion of 24 analyses. The time required by the "average" technician to carry out the different operations was as follows. enzyme hydrolysis 75 min, extraction procedure 120 min, colour development and colorimetry 95 min. Total 290 min.

Over-all yield As indicated, the present method has been evolved from that described by Beling (1963) which had been in use in this laboratory for several years. To compare the yields obtained by the two methods, four consecutive 24 hour urine specimens from 17 patients were analysed in parallel by both methods. The results obtained are indicated in Table II

An analysis of variance of the data of Table II reveals that the mean value ± the standard deviation (S.D) of a single estimate was 1..98 ± 4 71 mg using the method of Beling (1963) and 19 63 ± 2.77 mg by the use of the present method. Thus the proposed method gives a coefficient of variation (14 1) which is significantly smaller than that of the method employing gel filtration (36.3%) In addition the present method gives—on the average—50% higher estimates of the oestriol content of pregnancy urine specimens, than the method of Beling (1963). This difference is highly significant ($p < 0.001$)

Assessment of the reliability of the proposed method

Precision To evaluate the precision at different oestriol concentrations, 132 urine samples from 31 patients were analyzed in duplicate.

The standard deviations were calculated by the method of Snedecor (1952) It appears from the data of Tables III that the precision of the method is satisfactory

Accuracy This has been assessed following the addition of labelled as well as non-labelled oestriol conjugates to samples of cycle urine The results are shown in Table IV

Since 90 recovery was obtained following the addition of as little as 2.0 µg of oestriol glucosiduronate it is concluded that the accuracy of the method is satisfactory

Sensitivity The smallest amount of oestriol which can be estimated with confidence is around 2.0 µg/ml urine. Thus the method will yield reliable estimates of 2.0 mg oestriol per 24 hours or more

Specificity Prior to colorimetry some final fractions were subjected to gas chromatographic analysis following the formation of trimethyl silyl ethers. The chromatogram of a representative sample from late pregnancy urine is shown in Fig. 1

The retention time of peak no 3 was identical with that of oestriol trimethyl silyl ether It appears from the data of Fig. 1 that—in spite of the limited purification procedure employed—oestriol was the quantitatively most important constituent of the crude extracts studied.

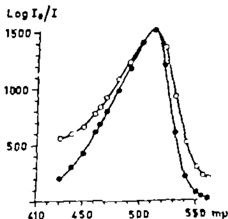


Fig Absorption spectrum of the Kober bromogens (method Nock 1961) formed from authentic oestriol (filled circles) and from the xtract of late pregnancy urine specimen (open circles), using the proposed method

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FIBRINOLYTIC ACTIVITY OF VEINS DURING PREGNANCY

Birger Astedt, Sune Isacson, Inga Marie Nilsson and Maurizio Pandolfi

From the Coagulation Laboratory (Head: Professor Inga Marie Nilsson) and the Department of Obstetrics and Gynaecology (Head: Professor Stig Kullander), Malmö General Hospital, University of Lund, Malmö, Sweden

Abstract The fibrinolytic activity of the blood progressively decreases during pregnancy and in the last month it is often barely demonstrable—not even after venous stasis. The fibrinolytic activity in the venous walls, as determined histochemically in venous biopsy specimens, is significantly reduced throughout pregnancy. It appears that the change in hormone balance during pregnancy results in reduction of the synthesis of activators in the vessel walls and/or inhibition of the release of such activators to the blood stream.

The occurrence of activators of fibrinolysis in the vessel walls was first perceived by Mole (1948). Using a histochemical method Todd (1959) showed that the activators are contained in the walls of small blood vessels and in the intima of large veins. In the superficial veins the activity is confined mainly to the vasa vasorum in the adventitia (Pandolfi et al., 1967). According to Fearnley (1965), activators are continuously liberated from the vessel walls and maintain the spontaneous fibrinolytic activity of the blood. Venous stasis can stimulate this release and thereby raise the activity in the blood (Clarke et al., 1960).

In pregnancy the fibrinolytic activity of the blood is decreased, as measured by clot lysis methods (for references see Nilsson & Kullander 1967). Brakman (1966) measured the spontaneous fibrinolytic activity in the blood in pregnant women by testing the plasma and resuspended euglobulin precipitate on fibrin plates and found it to be only slightly decreased. Using essentially the same method Nilsson & Kullander (1967) found the spontaneous fibrinolytic activity to decrease successively during pregnancy and to be barely demonstrable during the third trimester.

This paper reports an attempt to elucidate the discrepancy between the above, somewhat conflicting results. Further we thought that this possibly decreased activity might be caused by a low content of plasminogen activator in the vessel wall and/or by impaired release of this agent. We therefore studied the blood fibrinolysis after venous stasis and the vascular fibrinolytic activity in venous biopsy specimens from pregnant women.

MATERIAL AND METHODS

The clinical material consisted of 60 healthy pregnant women in various stages of pregnancy, 20 in each trimester.

Venous biopsy specimens, about 0.5 cm long, were obtained from the left lower arm under local anaesthesia. The fibrinolytic activity was demonstrated by the histochemical method of Todd (1959)—sections covered with a thin, stained fibrin layer—and assessed according to the grading used by Pandolfi et al. (1967). Control specimens were obtained from 20 healthy non-pregnant women of reproductive age. Comparisons between the fibrinolytic activity of different groups of veins were made by the Wilcoxon rank sum test.

Venous stasis was produced by wrapping cuffs round both upper arms and inflating them to a level between the systolic and diastolic blood pressure. The stasis was maintained for 20 min. Immediately before removal of the cuffs blood samples were obtained from the occluded veins. The fibrinolytic activity was determined by testing the plasma and resuspended euglobulin precipitate immediately on unheated fibrin plates expressed in mm² of lysis (Nilsson & Olow 1962). The mean value of the fibrinolytic activity after venous stasis found at our laboratory in 200 normal women is 240 with standard deviation of 129 (Robertson, unpublished data).

RESULTS

The marked fibrinolytic activity normally produced by venous stasis gradually decreased during pregnancy and at the end of the third trimester such

excretion in a particular subject, than to the relation of the excretion values of a subject to those found in a normal population. The same conclusion was reached by B.ling (1963) who found that the daily monitoring of oestriol excretion in high risk patients yielded very valuable information on foetal viability

Finally it may be questioned, whether or not the excretion of oestriol in pregnancy urine reflects the general condition of the foetus and that such assays can indeed confidently be used as an index of foetal viability The theoretical background of oestriol synthesis in the foeto-placental unit (i.e which r actions are carried out by the foetus, by the mother and by the placenta and to what extent) has been discussed in several recent reviews (Diczfalusy 1964 1967 1969 Diczfalusy & Benagiano 1966 Diczfalusy & Mancuso 1969).

ACKNOWLEDGEMENTS

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REFERENCES

Adlercreutz, H. Acta endocr (Kbh). Suppl. 72, 196_
Allen, W M J clin Endoc 10 71 1950.
Bauld, W S Biochem J 56. 4_6, 1954
— Biochem J 59 794, 1955
— Biochem J 63 488, 1956
Beling, C G Acta endocr (Kbh). Suppl. 79 1963
Breuer H I Research on Steroids (ed. C Cassano), ol. 1 p. 133 Il pensiero scientifico Rome 1964
Brown, J B Biochem J 60 185 1955
Brown, J B., Bulbrook, R. D & Greenwood, F C J Endocr 16 49 1957
Brown, J B & Coyle M. J Obst Gynaec Brit Clwth 70. 19 1963
Cohen, S. L. J cli Endocr & Metab 26. 994 1966
Dale E Greene J W & Duhring, J L. Amer J Obstet Gynec 9 11_ 1965
Diczfalusy E. Fed Proc _3 791 1964
— Acta endocr (Kbh) 0 16, 1955
— Mém Acad Roy Méd Belg II Sér 6 111 1967
— Excerpta Med International Congr Ser 111 ?1 196
Diczfalusy E. & Lindkvist, P Acta endocr (Kbh) _ ?1 1956.
Diczfalusy E. & Westman, A. Acta endocr (Kbh) 1 ?, 1956.
Diczfalusy E. & Lauritzen, C. Oestrogene beim Menschen. Springer Berlin, Göttingen and Heidelberg 1961.
Diczfalusy E., Barr M & Lind, J Acta endocr (K?) 46. 511 1964
Diczfalusy E. & Benagiano, G. In Research on Steroids (ed. C. Cassano), ol. 2, p. 77 Il pensiero scientifico Rome, 1966.
Diczfalusy E & Mancuso, S J Foetus and Placenta (ed. A. Klopper & E. Diczfalusy), p. 191 Blackwell Scientific Publications, Oxford and Edinburgh, 1969
Frandsen, V A. & Stakemann, G Acta endocr (Kbh) 44 183, 1963 a.
— Acta endocr (Kbh) 44 196, 1963 b
Furuhjelm, M. Acta obstet gynec scand 41 370, 196_
Goebelsmann, U Sjöberg, K., Wiqvist, N & Diczfalusy E. Acta endocr (Kbh) 50 261 1965 a.
Goebelsmann, U Eriksson, G Wiqvist, N. & Diczfalusy E.. Acta endocr (Kbh) 50 273, 1965 b.
Goebelsmann, U Diczfalusy E., Katz, J & Levitz, M Steroids 6 859 1965 c
Goebelsmann, U Cooke I., Wiqvist, N & Diczfalusy E.. Acta endocr (Kbh) 5 30 1966.
Goebelsmann, U Wiqvist, N. & Diczfalusy E. Acta endocr (Kbh) 59 595, 1968.
Greene, J W Smith, K., Kyle G C., Touchstone J C & Duhring, J L. Amer J Obstet Gynec 91 684, 1965
Hobkirk, R., Blahey P R., Alfheim, A., Raeside J I & Joron, G. E. J clin Endocr & Metab 20 805 1960
Klopper A. & Wilson, G J Obstet Gynaec Brit Cwlth 69 533 196_
Lisboa, B P Goebelsmann, U & Diczf lusy E Acta endocr (Kbh) 54 467 1967
Nocke W Biochem J 78 593 1961
Slaunwhite, W R., Jr Lichtman, M A. & Sandberg, A. A J clin Endocr & Metab 4 638 1964
Snedecor G. W Biometrics 8 85 query no 9_ 195_
Taylor E. S., Bruns, P D Duncan, I W & Drose V E Amer J Obstet Gynec 81 625 1961
Troen, P Nilsson, B Wiqvist, N & Diczfalusy E. Act endocr (Kbh) 38 361 1961
Vestergaard, P Acta endocr (Kbh) 8 193 1951
Zucconi, G Lisboa, B P Simonitsch, E Roth, L. H gen, A A & Diczfalus E Acta endocr (Kbh) 56 413 1967

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well as on the balance between these hormones in oral contraceptives.

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REFERENCES

Brakman, P Amer J Obstet Gynec *94* 14, 1966.

Breckenridge, R. T & Ratnoff, O. D.. New Engl J Med 270 298, 1964

Clarke, R L., Orlandi, A. & Clifton, E. E.. Angiology *11* 367 1960.

Drill, V A. & Calhoun, D W JAMA 206 77 1968.

Erichson, R. B New York St J Med 65 1091 1965

Fearnley G. R.. Fibrinolysis, p. 56. Williams and Wilkins, Baltimore 1965

Mole, R. H.. J Path Bact 60-413 1948.

Nilsson, I. M. & Kullander, S Acta Obstet Gynec Scand 46 273, 1967

Nilsson, I. M. & Olow B Acta Chir Scand *123* 247 196..

Owren, P A Ann Intern Med *63* 167 1965

Pandolfi, M., Nilsson, I. M., Robertson, B. & Isacson, S.. Lancet 2 127 1967

Shaper A. G., Kear J Macintosh, M., Kyobe, J & Njama, D.. J Obstet Gynaec Brit Comm *75* 433, 1968.

Taylor J J Postgrad Med J *41* 80, 1965.

Todd, A. S J Path Bact *78* 281 1959

Villamanta, U Amer J Obstet Gynec *93* 142, 1965

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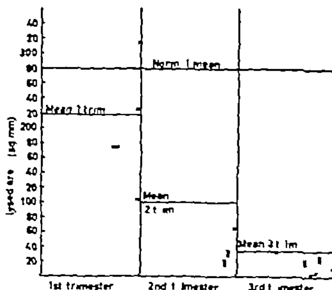


Fig 1 Fibrinolytic activity of venous blood from pregnant women after venous stasis in the arms (resuspended euglobulin precipitate Sq. mm of lysis on fibrin plates).

activity was often no longer demonstrable (Fig. 1) Only the results of tests with resuspended euglobulin precipitate on fibrin plates are included in the figure the tests with plasma having given the same results.

The activator of plasminogen in the venous wall was confined to the vasa vasorum in the adventitia. Throughout pregnancy the activator content proved significantly lower (1st trim. $P < 0.01$ 2nd and 3rd trim. $P < 0.001$) (Fig. 2) than in the controls. No significant differences were seen between the trimesters of pregnancy

DISCUSSION

The cause of this reduction of the fibrinolytic activity during pregnancy is obscure. It has not been possible to demonstrate any significant increase of the inhibitors of the fibrinolytic system during pregnancy (Nilsson & Kullander 1967). The reduced activator content in venous walls suggests that the hormonal changes during pregnancy are associated with a decreased synthesis of the fibrinolytic activators in the vessel walls. Compared with the low fibrinolytic activity in the blood especially during the last trimester however the activity in the vessel wall is so relatively high that the release of the activators into the blood stream is probably inhibited.

The demonstrated reduction of the fibrinolytic activity of the blood and low content of fibrinolytic activators in the vessel wall resemble those known to occur in thrombotic conditions (Pandolfi et al., 1967) but are more striking, especially the very low fibrinolytic activity during the third trimester of pregnancy Pregnancy has also been called a "hypercoagulable state" (Ericsson, 1965) But it has not been unequivocally proved that thrombosis really is more common during pregnancy (Taylor 1965 Breckenridge & Ratnoff, 1964 Villasanta, 1965 Drill & Calhoun, 1968).

That pregnant woman—with decreased fibrinolytic activator content in the venous walls and, at the end of pregnancy with barely any demonstrable fibrinolytic activity in the blood— do not have thrombosis appreciably more often than non-pregnant woman may to some extent be due to the fact that an important and possibly necessary factor in the initial phase of thrombus formation is increased platelet adhesiveness (Owren, 1965). During pregnancy however platelet adhesiveness is normal (Nilsson & Kullander 1967 Shaper et al., 1968 Astedt & Hedner unpublished data).

The above observations may perhaps prove useful in the investigation of problems bearing on the therapeutic use of oestrogens and gestagens as

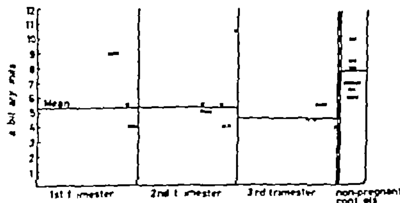


Fig Fibrinolytic activity of arm veins in pregnancy (histochemically determined. Arbitrary unit).

well as on the balance between these hormones in oral contraceptives.

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REFERENCES

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Breckenridge, R. T. & Ratnoff, O. D. New Engl J Med *270* 298, 1964.
Clarke, R. L., Orandi, A. & Clifton, E. E. Angiology *11* 367, 1960.
Drill, V. A. & Calhoun, D. W. JAMA 206, 77, 1968.
Erickson, R. B. New York St J Med *63* 1091, 1963.
Fearnley, G. R. Fibrinolysis, p. 56. Williams and Wilkins, Baltimore 1965.
Mole, R. H. J Path Bact 60 413, 1948.
Nilsson, I. M. & Kullander, S.: Acta Obstet Gynec Scand *46* 273, 1967.
Nilsson, I. M. & Olow, B. Acta Chir Scand *123* 247, 1962.
Owren, P. A. Ann Intern Med *63* 167, 1965.
Pandolfi, M., Nilsson, I. M., Robertson, B. & Isacson, S. Lancet 2 127, 1967.
Shaper, A. G., Kear, J., Macintosh, M., Kyobe, J. & Njama, D. J Obstet Gynaec Brit Comm *75* 433, 1968.
Taylor, J. J. Postgrad Med J *41* 80, 1965.
Todd, A. S. J Path Bact *78* 281, 1959.
Villasanta, U. Amer J Obstet Gynec *93* 142, 1965.

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THE VALUE OF LAPAROSCOPY IN THE DIFFERENTIAL DIAGNOSIS BETWEEN UTERINE FIBROMYOMATA AND ADNEXAL TUMOURS

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Abstract. Out of a total of 2098 laparoscopies, 90 (4.3%) were made to settle the diagnostic questions: I. fibromyomata of the uterus or adnexal tumour? and II. fibromyomata of the uterus concomitant with adnexal tumour or uterine fibromyomata only? A diagnosis was obtained in 83 patients (9[illegible]%). Adnexal disease was found in 28/83 (34%) and fibromyomata of the uterus only were present in 55/83 (66%). Neoplastic tumours were found in 19/83 (24%). Doubts regarding fibromyomata of the uterus versus adnexal disease can quickly be resolved by laparoscopy. Adnexal operations can be performed immediately after the laparoscopy. When only uterine fibromyomata are found that do not require surgery, exploratory laparotomy and unnecessary hysterectomies are avoided.

When patients with uterine fibromyomata diagnosed by bimanual palpation are kept under observation only, it is necessary to ensure that no ovarian neoplasm or other adnexal pathology exists which require surgical treatment.

The tumour or tumours felt should, as far as possible, be identified as uterine fibroids. Even if it is beyond doubt that the uterus contains fibroids, concomitant adnexal pathology requiring surgery or other treatment must be ruled out.

Such conclusions can often be made at bimanual palpation. Simple manoeuvres are sometimes useful, for instance, traction with a vulsellum on the cervix. Examination under anaesthesia often enhances palpation and should be performed in doubtful cases.

When normal ovaries are felt and the tumour or tumours together with the uterus form a single mass, the diagnosis of uterine fibroids can be considered safe, and gross adnexal pathology excluded. In elderly women with uteri of the type mentioned, expectancy is defendable also when it is impossible to feel the ovaries. At an advanced age, they may be too atrophic and thereby escape palpation.

On the other hand, besides a normal or fibroid uterus, one or several tumours are often felt laterally, their connection with the uterus being doubtful. It can be difficult to decide by means of bimanual palpation whether or not such tumours lateral to the uterus are subserous fibroids. The question can be settled when there is a characteristic stalk connecting the uterus and the tumour and also when normal ovaries are clearly felt.

In doubtful cases, as stated by among others, Sjövall (1950) and Frangenheim (1959), it is possible to make a firm diagnosis using coelioscopy and thus avoid exploratory laparotomy.

In order to test the diagnostic value of laparoscopy in the differential diagnosis: *fibromyoma of the uterus or adnexal tumour?* and *fibromyoma only or fibromyoma together with adnexal tumour?* 90 laparoscopic examinations on 89 patients were analyzed from a series of 2098 laparoscopies during the years 1961 to 1967. The frequency of the mentioned indications is 4.3% of the total number of laparoscopies. The papers by Sjövall (1963) and Samuelsson & Sjövall (1968) describe the technique. All members of the staff are trained to perform laparoscopy. Hence, many different surgeons are responsible.

Seven laparoscopies, about 8%, yielded no information: inspection was impossible owing to structures blocking the view.

In one instance, because of trouble with the anaesthesia, only intestines were seen. A second laparoscopy revealed fibromyomata only.

In one patient, a large fibromyomatous uterus blocked

cystoma, large as a grape, had evidently developed during the delay. One of the bilateral ovarian fibromas was seen at laparoscopy and interpreted as a "greyish-white ovarian tumour". The granulosa cell tumour was deemed to be ovarian tumour at the side of a fibromyomatous uterus. At operation, no fibromyoma was found.

III. *Adnexal pathology only*

Those 18 patients who at laparoscopy showed adnexal disease only and no fibromyomata all had a laparotomy. According to the findings at operation and histological examinations, they can be grouped as follows:

A. Ovarian endometriosis, 5 patients.
B. Ovarian cystomata, 7 patients.
C. Solid adnexal tumours, 6 patients.

The cases of *ovarian endometriosis* were chocolate cysts of which 3 were bilateral. The correct diagnosis was made by the laparoscopist in 2, the other 3 were labelled ovarian tumours without *further specification*.

Of the *cystomata* 3 were simple benign cysts, one being a benign pseudomucinous cystadenoma, another papillary serous benign cystoadenoma. Two were benign teratomata, one an ordinary dermoid cyst, the other a struma *ovarii*.

The laparoscopists stated the cystic nature of these ovarian tumours in five cases only.

Of the *solid adnexal tumours* one was a parovarian fibromyoma and the other 5 were ovarian tumours. Of these, one was a fibroadenoma, one fibromyoma, 2 were fibromas, and one thecoma. One of the fibromas had twisted stalk, and haemorrhagic infarction was seen at laparoscopy. The other fibroma was exactly diagnosed as such by the laparoscopist. The thecoma was interpreted as granulosa cell tumour because of the vascularity and the yellowish surface. The remaining three were diagnosed as ovarian tumours.

DISCUSSION

A stated in the introductory remark to this paper bimanual examination is of limited value in the differential diagnosis between fibromyomata of the uterus, on one hand, and adnexal tumour and fibromyomata of the uterus together with adnexal tumour on the other.

By using various X-ray methods—plain X-ray pictures, hysterosalpingo-pelvi-graphy (Kjellberg, 1942) gynaecography (Schultz & Rosen, 1961) and angiography (Borell Fernström, Lindblom & Westman, 1952)—the diagnostic procedure can be improved.

Direct coelioscopic inspection, however in most instances permits a quick and firm diagnosis.

Although laparoscopy seldom provides exact information as to the kind of adnexal tumour it gives enough to decide whether or not the patient should be operated upon.

In 1/3 of the cases (28/83) where the condition of the uterus and the adnexa could be judged, laparoscopy revealed adnexal disease: 2/3 were neoplastic tumours (19/28), one of them being malignant.

In 2/3 of the cases (55/83) where the uterus as well as the adnexa could be interpreted by laparoscopy fibromyomata of the uterus only were found without adnexal disease. Consequently with a fair degree of safety those 55 patients could be advised observation only. *Eight of these 55* who underwent laparotomy for various reasons had normal ovaries. In the remaining 47 patients, who were either observed by doctors or written to, there has been no evidence of adnexal involvement. One patient, however had a parovarian cyst removed afterwards. Those patients who have a fibromyomatous uterus where concomitant adnexal tumour might also be present are saved from an unnecessary operation by laparoscopy.

Both with regard to making swift diagnosis and allowing early operation for adnexal tumours, as well as permitting the observation of patients with fibromyomata who do not require major surgery laparoscopy is a valuable procedure.

REFERENCES

Borell, U. Fernström, I. Lindblom, K. & Westman, A. Acta Radiol (Stockholm) 38 247 1952.

Frangenheim, H. Die Laparoskopie und die Culdoskopie in der Gynäkologie. Thieme Verlag, Stuttgart, 1959.

Kjellberg, S. R. Acta Radiol (Stockholm), Suppl. 43 1942.

Samuelsson, S. & Sjövall, A. Acta Obstet Gynec Scand 47 50 1968.

Schultz, E. & Rosen, Saul W. Amer J Roentgenol 86: 866, 1961.

the view of the ovaries. Laparotomy immediately performed revealed, besides the fibromyoma, ovarian endometriosis and a dermoid cyst.

In the remaining 5 patients, adhesions blocked the view. All were immediately operated upon. The findings were:

1 Ovarian carcinoma and metastases.
Simple benign ovarian cystomata.
3 Fibromyoma of the uterus and ovarian endometriosis.
4 Ovarian endometriosis.
5 Adenomyosis of the uterus.

There remain 83 laparoscopic examinations in 83 patients where the diagnostic accuracy can be evaluated in regard to the condition of the uterus as well as that of the adnexal structures.

Regarding the laparoscopic diagnoses those 83 examinations belong to 3 principal groups.

I Fibromyomata of the uterus 55 (66%).
II Adnexal pathology and fibromyomata of the uterus 10 (12).
III. Adnexal pathology only 18 (22%)

I *Fibromyomata of the uterus only*

Of those 55 patients where only fibromyomata of the uterus were found, 8 underwent laparotomy one patient immediately

When the laparoscopic examination began, sarcoma was suspected; a needle biopsy was made from one of the fibroids in the uterus. Pulsating bleeding from the needle-prick continued. Laparotomy revealed only fibromyomata. The postoperative course was uneventful.

The other 7 patients were first kept under observation. Two had their operations after 2 and 4 years, respectively as the tumours substantially increased in size Three underwent surgery after 3 to 4 years for bleeding and _ after _ and 5 months for urinary trouble. Normal ovaries on both sides had been seen by the laparoscopist in 3 of these 7 patients. In 3 other patients only the ovary of one side had been visualized, and in 1 patient, the ovaries had not been inspected. The presence of ovarian tumours had been regarded as improbable In these 7 cases normal ovaries were found at laparotomy and the laparoscopic diagnosis fibromyoma was confirmed.

In 46 of the 47 patients who most of them for several years since laparoscopy were kept under observation only both ovaries were judged normal at the laparoscopic examination. In one patient, only one of the ovaries could be inspected. but the presence of ovarian tumour on the other side was regarded highly improbable. This patient, 3 years after laparoscopy showed the same finding as before on bimanual examination. She is one of 35 who have been regularly followed up at the department or by other gynaecologists and have remained well. One patient died one year after laparoscopy from intercurrent disease. Autopsy revealed a fibromyomatous uterus, normal ovaries, and the malignant lymphoma that caused her death.

Eleven patients who did not report for follow-up examinations were sent letters with a questionnaire. One has not replied. The other 10 had no complaints that gave rise to any suspicion of intrapelvic complications. Recently one patient had a laparotomy and was found to have a para-ovarian cyst.

II *Adnexal pathology and fibromyomata of the uterus*

All 10 patients in whom the laparoscopic diagnosis was fibromyoma of the uterus and some kind of adnexal disease had a laparotomy In 4 patients the adnexal disorder was non-neoplastic:

1 Non-specific salpingitis.
2. Salpingitis (and tubal endometriosis).
3 Bilateral hydro-salpinx.
4 Tubo-ovarian endometriosis.

The tubo-ovarian endometriosis and the hydrosalpinges were exactly as diagnosed by the laparoscopists. The cases of salpingitis were thought to be a cyst" and "endometriosis with inflammation"

The remaining 6 patients at operation showed neoplastic ovarian tumours:

1 Dermoid cyst.
_ Dermoid cyst – serous cystoma.
3 Simple cystoma.
4 Serous cystoma.
5 Ovarian fibromyoma, bilateral.
6. Granulosa cell tumour

Three were judged at laparoscopy to be ovarian cyst" (1), cyst (3 4), one as greyish-white ovarian tumour (5). The dermoid and serous cystoma ( ) was misinterpreted as a unilateral ovarian fibroma The other ovary looked quite normal. This patient did not give her consent to operation until three years later when the "fibroma" proved to be a dermoid cyst. The serous

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PLACENTOGRAPHY BY ULTRASOUND

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From the Department of Obstetrics and Gynaecology (Head Professor Alf Sjövall)
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Abstract The placental location and the boundaries of the placenta were established by two-dimensional ultrasound examination in 107 cases. In 45 of them, the result of the ultrasound placentography was correlated with the finding at Caesarean section The reliability of the ultrasound method was 95.6% figure comparable with those produced by other techniques The technique of ultrasound placentography is simple, the method does not cause any discomfort for the patient and is harmless to mother and child.

The diagnostic value of ultrasound examination in obstetrics and gynaecology is now well documented (Donald et al 1958, 1960 1961 1967 Donald, 1967 Gottesfeld, 1966 Kossoff et al 1965 Sundén, 1964, 1965 1967 1968 Taylor et al 1964 Thompson et al 1965) One of the factors that makes ultrasound examination valuable in obstetrics is that the abdomen in pregnant women, for a variety of reasons, has proved to be particularly suitable for this investigation method. During pregnancy the uterus forces the strongly sound reflecting loops of bowel away from the investigation area and th. anatomical configuration becomes ideal for examination with ultrasound The uterus also contains the amniotic fluid, almost homogeneous from the standpoint of ultrasound, which with its good sound transmission creates optimum conditions for echo recording from intra-uterine structures. The results from large animal experimental and clinical series show that the diagnostic use of pulsating ultrasound of low intensity creates no risk for mother or f tus, hereas X-ray and isotope examination expose the tissues to ionizing radiation (Andrew 1964 Donald, 1964 Gottesfeld, 1966 Smyth, 1964 Sundén, 1964 Taylor et al 1964).

The knowledge of the precise location of the placenta in cases of suspected placenta praevia and b-fore amniocentesis in patients with Rh-immunization is of the utmost importance The present methods of directly or indirectly deter mining the position of the placenta by X-ray placentography produce reliable results in 95–97% (Borell et al., 1963 Sutton, 1966 Visscher & Baker 1960). Soft tissue radiography gives poor results in cases of polyhydramnios and the position of the placenta can be difficult to determine in the presence of multiple pregnancy or transverse lie f the foetus. On the other hand, ar teriography permits the determination of the placental position independent of the position of the foetus or the presence of polyhydramnios (Borell et al., 1963) Weinberg et al (1963) consider that X-ray determination of the position of the placental site produces the best results after the 35th week of pregnancy whereas the reliability is less between the 28th and 35th week of pregnancy Using arteriography Borell et al. (1963) obtained diagnostic reliability of 97% irrespective of the length of the pregnancy

Placentography with isotopes gives a diagnostic reliability of 95–98% (Cavanagh et al., 1961 Hibbard, 1961 Johnson, 1966, Visscher et al 1960 Weinberg et al., 1963).

Birnbaum & Kliot (1965) could, with the use of thermography localize the placenta in 96% of the cases, but they point out the difficulties with this method when the placenta is situated posteriorly Reynolds et al. (1967) state, on the contrary that thermography is not a reliable method of placental localization.

Every form of ionizing radiation during preg nancy carries the risk of genetic injury to the foe tus. Some X-ray techniques are not applicable for routine use in all hospitals, moreover during

Sjövall, A. Fifth Meeting of the Northern Association of Obstetrics and Gynaecology 1948, p 288 Lund, 1950.
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Abstract The placental location and the boundaries of the placenta were established by two-dimensional ultrasound examination in 107 cases. In 45 of them, the result of the ultrasound placentography was correlated with the finding at Caesarean section. The reliability of the ultrasound method was 95.6%, figure comparable with those produced by other techniques. The technique of ultrasound placentography is simple, the method does not cause any discomfort for the patient and is harmless to mother and child.

The diagnostic value of ultrasound examination in obstetrics and gynaecology is now well documented (Donald et al., 1958 1960 1961 1967 Donald, 1967 Gottesfeld, 1966 Kossoff et al 1965 Sundén, 1964, 1965 1967 1968 Taylor et al 1964 Thompson et al., 1965). One of the factors that makes ultrasound examination valuable in obstetrics is that the abdomen in pregnant women, for a variety of reasons, has proved to be particularly suitable for this investigation method. During pregnancy the uterus forces the strongly sound reflecting loops of bowel away from the investigation area and the anatomical configuration becomes ideal for examination with ultrasound The uterus also contains the amniotic fluid, almost homogeneous from the standpoint of ultrasound, which with its good sound transmission creates optimum conditions for echo recording from intra-uterine structures. The results from large animal experimental and clinical series show that the diagnostic use of pulsating ultrasound of low intensity creates no risk for mother or foetus, whereas X-ray and isotope examination expose the tissues to ionizing radiation (Andrew 1964 Donald, 1964 Gottesfeld, 1966 Smyth, 1966 Sundén, 1964 Taylor et al., 1964).

The knowledge of the precise location of the placenta in cases of suspected placenta praevia and before amniocentesis in patients with Rh-immunization is of the utmost importance The present methods of directly or indirectly determining the position of the placenta by X-ray placentography produce reliable results in 95–97% (Borell et al., 1963 Sutton, 1966 Visscher & Baker 1960). Soft tissue radiography gives poor results in cases of polyhydramnios and the position of the placenta can be difficult to determine in the presence of multiple pregnancy or transverse lie of the foetus. On the other hand, arteriography permits the determination of the placental position independent of the position of the foetus or the presence of polyhydramnios (Borell et al., 1963). Weinberg *et al* (1963) consider that X-ray determination of the position of the placental site produces the best results after the 35th week of pregnancy whereas the reliability is less between the 28th and 35th week of pregnancy Using arteriography Borell et al (1963) obtained a diagnostic reliability of 97% irrespective of the length of the pregnancy

Placentography with isotopes gives a diagnostic reliability of 95–98% (Cavanagh et al., 1961 Hibbard, 1961 Johnson, 1966 Visscher et al., 1960 Weinberg et al., 1963)

Birnbaum & Kliot (1965) could, with the use of thermography localize the placenta in 96% of the cases, but they point out the difficulties with this method when the placenta is situated posteriorly Reynolds et al. (1967) state, on the contrary that thermography is not a reliable method of placental localization.

Every form of ionizing radiation during pregnancy carries the risk of genetic injury to the foetus. Some X-ray techniques are not applicable for routine use in all hospitals, moreover during

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Fig.   Transverse scan.



Fig. 4. Posterior placenta praevia. Same case as in Fig. 3. The sensitivity is reduced by 20 dB.

the basic principles for diagnostic use of ultrasound and the two-dimensional echo-recording have been described earlier (Donald, 1958; Sundén, 1964). When the ultrasound beam passes into the body and there meets tissues with various acoustic properties, some of the energy will be reflected from the interfaces between the tissues in the form of echoes, whose strength is due more to differences in the substances on both sides of the interface than to the tissues themselves. The reflected sound is recorded two-dimensionally via a cathode ray tube on Polaroid film in the form of a cross-section of the sound-reflecting interfaces in the region under examination.

At the examination, the patient lies on a couch or in her bed. A thin layer of oil on the skin of the abdomen eliminates sound-reflecting air bubbles. For complete exploration of the uterus the probe, with the sound generating and echo receiving crystal, is moved, during simultaneous rocking, longitudinally or transversely over the abdomen in planes lying close to one another. The examination takes 20–30 min (Fig. 2).

The placenta is a soft tissue structure rich in blood vessels with very good sound transmitting properties. High amplification is therefore required to reveal it. The sensitivity of the apparatus is adjusted by altering the transmitter output power which is expressed in decibels (dB). The sensitivity control operates in a series of steps from 10, which is maximum output power, to 0. Each step changes the sensitivity by the same amount, i.e. 5 dB. Sensitivity less than maximum output power is expressed as minus quantities; most placentas are revealed at minus 10–15 dB. The placenta appears on the ultrasound picture as an area situated close to the uterine wall and contains a varying amount of small echoes (Fig. 3). When the amplification is reduced—in this case by 20 dB—the placenta is not detected and is replaced by an echofree area (Fig. 4).

Where there is relatively much amniotic fluid between the foetus and the foetal surface of the placenta, the echo line from the foetal placental surface appears, despite low amplification (Fig. 5).

The placenta can be localized early in pregnancy, as in Fig. 6, from the 16th week of pregnancy.

To obtain precise determination of the extent of the placenta, both longitudinal and transverse pictures are necessary (Figs. 7 and 8).



Fig.   Posterior placenta praevia. Pregnancy at 28th week. Longitudinal scan. Arrows indicate margins of placenta. H, Foetal head.



Fig. 5. Anterior placenta. Pregnancy at 36th week. Longitudinal scan. Arrows point to the margins of the placenta. AF, Amniotic fluid. Contour of foetal head on right.

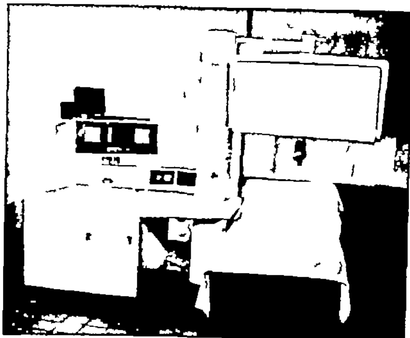


Fig 1 Ultrasonic scanning machine.

certain of these investigations the patients are ex posed to some discomfort.

A relatively simple and reliable—as well as harmless—method for determining the position of the placenta can b. particularly valuable. During recent years, tests have been made with various ultrasound methods. The one-dimensional ultra sound m-thod does not give any information concerning which structure(s) cause the echoes, and the echo-pattern on the oscillograph screen changes with the change of angle of incidence of the sound. The placenta is often thin in the periphery and the difficulty of "seeing" the placenta here by this method is obvious. Kratochwil (1968) states that with the one-dimensional method, wher a vaginal probe was also used, he could determine the position of the placenta in 98% of the cases. He points out that the localization of a completely posteriorly situated placenta is not possible by this method, which could other wise be used from the 18th–20th week of pregnancy

With the use of the Doppler-effect, Bishop (1966) and Brown (1967) could determine the position of the placenta in 78% and 91% respectively of the cases Hunt (1969) in 55 out of 56 cases, could determine the position of the placenta correctly as far as the uterine segment was concerned. By this method, it is easy to establish whether the foetal heart beats, but the qualitative difference between the reflected sound from the circulation in the uterus, in the umbilical cord, and in the placenta is most often very small and the opinion of myself and others (Donald & Abdulla, 1968) is that this method is unreliable and should not be used for localization of the placenta.

For the exact localization and photographic recording of the entire placenta in relation to the foetus and the uterine wall a two-dimensional method is necessary The first two-dimensional ultrasound pictures of the placenta were published at the end of 1966 and the beginning of 1967 by Gottesfeld et al. (1966) Donald & Abdulla (1967) and Sundén (1967) The reliability is stated by Gottesfeld et al. (1966) to be approximately 97% but they point out that in many cases of posteriorly situated placenta no typical ultrasound picture was obtained instead the position of the placenta had to be determined by elimination. Donald & Abdulla (1968) reported more than 94 reliability and in our first series the corresponding figure was 97 (Sundén, 1968).

In the longitudinal scans the patient's head is to the left of the picture. In the transverse scans the patient is seen from below and the patient's right side is on the left of the picture.

METHOD

The apparatus used since 1962 at the Department of Obstetrics and Gynaecology in Lund (Fig. 1) is constructed by Smith's Industrial Division in Glasgow and

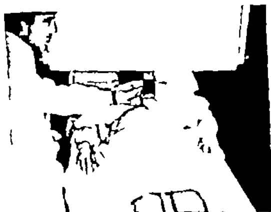


Fig. 2. Transverse scan.



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Fig. [illegible] Posterior placenta praevia. Pregnancy at 28th week. Longitudinal scan. Arrows indicate margins of placenta. H, Foetal head.



Fig. 5. Anterior placenta. Pregnancy at 36th week. Longitudinal scan. Arrows point to the margins of the placenta. AF, Amniotic fluid. Contour of foetal head on right.



Fig 6 Posterior placenta. Pregnancy at 16th week. Longitudinal scan. Arrows indicate placenta.



Fig 8 Anterior placenta. Same case as in Fig. 7 Transverse section at umbilical level. P Placenta.

RESULTS

The investigations made during the period from the end of 1966 up to and including January 1969 comprise 107 cases. The indications for ultrasound placentography are shown in Table I, and the gestation period at the time of investigation in Table II

For practical reasons predictions of the placental site have been classified as follows: anterior anterior lateral anterior fundal, posterior posterior lateral posterior fundal, low lying and placenta praevia.

For appraisal of the reliability of the ultrasound placentography we have preferred palpation and direct inspection of the placenta in situ at Caesarean section as a more accurate method for determining the location of the placenta than manual exploration at delivery per vias naturales, when the placenta is often completely or partly detached.



Fig 7 Anterior placenta. Pregnancy at 35th week. Longitudinal scan. P Placenta, H, Foetal Head.

Analysis of the predictions of the position of the placenta is given in Table III. Of the 107 cases, Caesarean section was performed in 45 The correlation between the ultrasound placentography and the finding at Caesarean section is shown in Table III Ultrasound diagnosis was wrong in 2 of the 45 cases. This is an error rate of 4.4% In 1 case where the ultrasound picture showed the placenta situated dorsolaterally the placenta was found to be located anteriorly at Caesarean section. The other case is referred to under the heading of placenta praevia.

In 22 cases where the position and extension of the placenta was determined at Caesarean section, both X ray examination and ultrasound placentography had been carried out. Of these, 2 cases were diagnosed incorrectly by X ray (angiography) but correctly by ultrasound, and in 1 case, the X ray diagnosis was correct and the ultrasound diagnosis wrong.

In the remaining 62 cases delivered vaginally the result of the ultrasound examination was in

Table I. *Ultrasound placentography*

Indications	No. of cases
Antepartum haemorrhage	51
Unstable lie	22
Suspicion of twins	15
Toxaemia	8
Amniocentesis	4
Elective Caesarean section	4
Diabetes	2
Legal abortion sterilisation	1
Total	107

Table II. *Time of ultrasound diagnosis*

Weeks since L.M.P. at time of ultrasound placentography	Ultrasound diagnosis: No. of cases	Later Caesarean section
16	2	1
24	1	
26	2	1
27	1	
28	1	1
29	4	3
30	4	
31	2	1
32	7	2
33	6	3
34	10	4
35	13	3
36	13	5
37	18	8
38	12	7
39	7	6
40	4	
Total	107	45

no case contradicted by the clinical course at delivery.

Placenta praevia

The series included 8 cases of placenta praevia. Here, the ultrasound diagnosis was correct in 7. In 1 case—examined in the 29th week of pregnancy—the low lying placenta, dorsally on the ultrasound picture, was judged not to reach below the foetal head, but at Caesarean section, it was found to cover 1/3 of the internal os. This was the only false negative result. No false positive



Fig. 9. Posterior placenta praevia. Pregnancy at 35th week. Longitudinal scan. Transverse presentation with contour of foetal body in the middle of the uterus. P Placenta.

diagnoses of placenta praevia were made in the other 99 cases. The ultrasound diagnosis of placenta praevia was made in the 7 correct cases between the 26th and 38th week of pregnancy. In 4 of these, the placenta was located on the dorsal wall. Fig. 9 shows the ultrasound picture of a type IV posterior placenta praevia.

Antepartum bleeding in the 33rd week of pregnancy led to the examination of a patient, whose result is seen in Fig. 10. This shows a type IV anterior placenta praevia.

DISCUSSION

Contrary to other techniques, the two-dimensional ultrasound examination visualizes the entire placenta, which is seen in its relation to the uterine wall and the foetus. The ultrasound picture of the placenta is usually so clear that no difficulties are encountered in interpreting the pictures. The

Table III. *Position of placenta at ultrasound examination and at Caesarean section*

Position of placenta	Ultrasound diagnoses: No. of cases	No. of Caesarean section	Diagnoses at Caesarean section (no. of cases)
Anterior	34	16	17
Anterior lateral	23	4	4
Anterior fundal	2	1	1
Posterior	14	6	6
Posterior lateral	11	3	2
Posterior fundal	12	6	6
Low lying	4	2	1
Placenta praevia	7	7	8
Total	107	45	45



Fig. 10. Anterior placenta praevia. Pregnancy at 34th week. Longitudinal scan. P Placenta extending down the anterior uterine wall in front of foetal head. Arrows point to the margins of the placenta.

echo density in dorsally situated placentas, despite high amplification, can be low due to absorption of the sound as the result of passage of the sound beam through the foetal body or foetal head. This is particularly evident at the end of pregnancy but there is usually no difficulty in indicating the margins of the placenta.

Gottesfeld et al (1966) thought that a completely dorsally located placenta could only be diagnosed by elimination if the periphery of the placenta did not reach one side of the uterus. The present investigation similar to others (Donald & Abdulla 1968 Sundén, 1968) has shown that a *completely dorsally situated placenta also can* be visualized by the two-dimensional ultrasound method

No preparation of the patient who can be examined in bed is necessary Contrary to some X ray methods, the ultrasound examination does not cause the patient any discomfort whatever and the method is in no way harmful to mother or child

REFERENCES

Andrew D S. Brit J Radiol *37* 185 1964

Birnbaum, S. J & Kliot, D A. Obstet Gynec (NY) *25* 515 1965

Bishop, E. H Amer J Obstet Gynec *96*, 863 1966.

Borell, U Fernstrom, I. & Ohlson, L. Amer J Obstet Gynec *86* 535 1963

Brown, R. E. Radiology *19* 828 1967

Cavanagh, D Powe, Ch. E. & Gilson, A. J Obstet Gynec (NY) *18* 403 1961

Donald, I. Med Biol Illus *14* 216, 1964

— Year Book of Obstetrics and Gynecology (ed. J P Greenhill), p. 243 Chicago, 1967 1968.

Donald, I., MacVicar J & Brown, T G Lancet *1* 1188, 1958.

Donald, I & Brown, T G. Proc. III Int. Conf p. 458 Medical Electronics, London, 1960.

— Brit J Radiol *34* 539 1961

Donald, I. & Abdulla, U Ultrasonics *5* 8, 1967

— J Obstet Gynaec Brit Comm *75* 993 1968.

Gottesfeld, K. R *Diagnostic Ultrasound (ed. Ch Grossman, J Holmes, C Joyner & E Purnell)*, p 428 Plenum Press, New York, 1966.

Hibbard, B M. J Obstet Gynaec Brit Comm *68* 481 1961

H nt, K. M J Obstet Gynaec *Brit Comm 76 144 1969*

Johnson, P M Sciarra, J J & Bragg, D Amer J Roentgenol 96, 677 1966.

Kossoff, G Garret, W J & Robinson, D E. Ultrasonic Energy (ed. E Kelly) p 365 Urbana, Ill. University of Illinois Press, 1965

Kratochwil, A. Ultraschalldiagnostik in Geburtshilfe und Gynäkologie, p 49 Stuttgart, 1968

Reynolds, W A., Ayers, M A. & Parker G. M Radiology *19* 825 1967

Smith, M G Diagnostic Ultrasound (ed. Ch. Grossman, J Holmes, C. Joyner & E. Purnell) p 296. Plenum Press, New York, 1966.

Sundén, B Acta Obstet Gynec Scand *43*. Suppl. 6, 1964.

— *J* Obstet Gynaec Brit Comm *72* 952, 1965

— Ultrasonics *5* 67 1967

— 15th Congress of the Northern Association of Obstetrics and Gynaecology Stockholm, 1968.

Sutton, D Brit J Radiol *39* 47 1966.

T ylor E. S., Holmes, J H Thompson, H. E. & Gottesfeld, K. R. Amer J Obstet Gynec *90* 655 1964

Thompson, H. E., Holmes, J H., Gottesfeld, K. R. & Taylor E. S. Amer J Obstet Gynec *92* 44 1965

Visscher R. D & Baker W S. Amer J Obstet Gynec *80* 1154 1960.

Weinberg, A., Shapiro, G & Bruhn, D F Amer J Obstet Gynec *87* 203 1963.

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MEMBRANE-LIKE STRUCTURES IN THE UTERINE CAVITY

A Hysterographic Study

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Abstract (1) In a series of 6 000 hysterograms 23 cases of thin regular membrane-like structures in the uterine cavity were found. They were situated either in the upper or lower part of the cavity and were 1 2 mm thick. (2) The membranes were found mostly in the secretory phase. They were in some cases present on one examination but absent on the following, with no intervening surgery. They were also found to disappear spontaneously during one examination. (3) Two cases of extensive irregular filling defects in the uterine cavity seen at hysterography are described. These defects had the characteristics generally ascribed to adhesions, yet in 1 case they were seen to disappear during the course of a single examination, and in the other case they were found to have disappeared from one examination to the next without intervening surgery. (4) It is stated that these defects are of functional and not organic nature. The diagnosis of adhesions cannot, therefore, be based on one hysterography alone, but requires confirmation of some kind.

Hysterosalpingography occasionally reveals thin regular membranes in the uterine cavity. The published reports of this phenomenon appear to be very scarce; the only descriptions we have found are those by Asplund (1952) and Rozin (1965). The former interprets this formation as a stricture, the latter as a segmental contraction. Rozin also cites Jarcho, who reported the phenomenon in 1931.

We have encountered these structures in 23 cases. Since we have noted certain features concerning their nature, we feel there is some reason to present an account of the material gathered.

In 1964 Zondek & Rozin published an investigation making clear that intrauterine filling defects thought to be typical of adhesions could disappear after denervation of the uterus or cutting of the myometrium.

The discovery of the inconstancy of such defects brings the hysterographic diagnosis of intrauterine adhesions into a completely new light: we can no longer take it for granted that defects with all the characteristics of adhesions are in fact adhesions, for they might just as well be contractile, functional structures instead. We have encountered two instances of defects which we first adjudged to be typical adhesions but which later were found to disappear spontaneously. Therefore, they seem to be of the same nature as the regular membranes previously mentioned. A description and discussion of these 2 cases follows.

TECHNIQUE

All hysterosalpingographies were performed with Schultze's instrument without using a manometer. Premedication of 1 ml omnopon-scopolamine was administered 1 hour before the examination. General anesthesia was not given. The contrast medium used was water-soluble; since the middle 1950s Peryodal H (Pharmacia) has been used exclusively. The contrast medium was injected slowly by hand under fluoroscopic control until the whole cavity was filled. The following pictures were taken: postero-anterior, right posterior oblique, left posterior oblique, lateral and antero-posterior. In order to maintain an even degree of filling of the cavity a small amount of contrast medium, usually 0.1–0.5 ml, was injected just before each exposure. The total amount of contrast medium used for one examination thus varied between 10 and 20 ml.

Hysteroscopy was also performed in some cases. In cooperation with Dr Karin Edström of the Department of Women's Diseases, one of us (Fernström) has developed a technique making use of an 8 mm hysteroscope (Storz) with a channel for flushing and a Hopkins optical system. The cavity is first washed with physiologic saline and then filled with Peryodal Viskös. The optic properties of this medium are suitable for hysteroscopy and its viscosity



Fig 1 Hysterogram. Upper membrane in left uterine cornu (arrow).

permits a controllable low degree of distension of the cavity enabling inspection of all its parts, including the uterine cornua.

MATERIAL

The series consists of 23 cases with *regular membrane-like structures* obtained from an analysis of about 6 000 hysterograms made at the Radiological Department of Karolinska sjukhuset during the years 1948–1957 Fourteen cases were examined once, 6 cases twice cases three times and 1 case 4 times, making a total of 36 hysterographies. Ten of these were made in the prolifera-

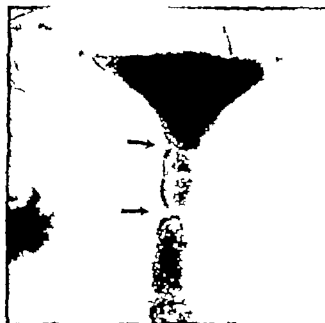


Fig 2 Hysterogram. Lower membrane (upper arrow) and the sphincterlike structure t the anatomical internal os (lower arrow).



Fig 3 Hysterogram: Three upper membranes in left uterine cornu (arrows).

tive phase, 25 in the secretory phase In 1 case the menstrual phase could not be determined. In the 9 cases on which two or more examinations had been made, the interval between examinations was at least 1 year in 6 cases, while for each of the three remaining cases the interval was 2 weeks, one examination having been performed in the proliferative phase and the other in the secretory phase The ages ranged between 4 and 47 years. The clinical diagnoses were infertility (13 cases), menometrorrhagia (3 cases), recurrent abortion (6 cases), and amenorrhea in 1 case Twelve patients were nulliparous, the remainder having borne one or more children.

The series also includes further cases with *irregular membrane-like structures* The preliminary diagnosis was adhesions, but they disappeared spontaneously

RESULTS

A. Regular membrane-like structures

The structures were seen in the upper part (Fig. 1) or in the lower part of the cavity (Fig 2) In the following description the former will be called Upper Uterine Membranes (UUM), and the latter Lower Uterine Membranes (LUM) Eight cases had only upper membrane-like structures of which 2 were bilateral. One of the latter two had no



Fig. 4 Hysterogram made in proliferative phase. All pictures taken during the same examination. (a) At the beginning of the examination. Lower membrane is well seen (arrow). (b) One minute after. The membrane is less pronounced (arrow). (c) Three minutes after. The membrane has disappeared, leaving only a small ridge at the left side (arrow).

less than three UUM on one side and one on the other side (Fig. 3). LUM only were seen in 14 cases. In 1 case there was a simultaneous occurrence of upper and lower membranes. The total number of membranes was 28.

The structures were remarkably uniform from 1 case to another. They were located in a plane perpendicular to the longitudinal axis of the cavity or of the uterine cornua. Their thickness was 1 mm, increasing slightly towards the uterine wall. The diameter of the membranes was: upper membranes average 10.5 mm (range 7–15 mm), and lower average 7.0 mm (range 5–11 mm). We have not been able to demonstrate a central hole directly on the pictures, but it is large enough to permit unimpaired filling of the part of the cavity above it.

Upper and lower membranes were seen in 26 hysterograms. In 23 of these the patient was in the secretory phase of the cycle and in all pictures the membranes were quite distinct in all views. In the remaining 3 the patient was in the proliferative phase of the cycle. The appearance of the membranes in the latter 3 hysterograms deviated from that seen in the secretory phase. In two of them the membranes disappeared during the examination (Fig. 4) and in the third case it was seen less distinctly than those in the secretory phase.

The "tubal sphincters" are located between the intramural part of the tube and the cavity of the uterus. The distance between the "tubal sphincters" or the place corresponding to their site and the upper membranes was in all cases more than 10 mm. The average distance between the upper border of isthmus and the lower membranes was 27 mm. The shortest distance measured was 15 mm.

In 7 of the 9 cases with upper membranes "tubal sphincters" were present at the same time. In 4 of the 15 cases with lower membranes sphinc-



Fig. 5 Hysterograms from 1 case examined on two occasions. (a) Secretory phase. Upper membrane in left uterine cornu (arrow). (b) Proliferative phase 2 weeks after a.

ter-like structures in the isthmus were present. In these 15 cases "tubal sphincters" were seen on 3 occasions. Therefore there seemed to be a good correlation between the presence of "tubal sphincters" and uterine membranes.

Two or more hysterographies were performed in 9 cases. In 6 of these upper membranes were seen on the first examination but not on the second. Two of these are particularly interesting in that only 2 weeks elapsed between the first and the second examination performed in the secretory and proliferative phase respectively with no intervening surgery (Fig. 5). In 2 cases the membranes were seen on both occasions. One patient, who was examined three times, exhibited membranes on the second occasion only (Fig. 6).

No membranes were seen in 10 of the 36 hysterograms. It is interesting to note that 7 of these were performed during the proliferative phase. Anomalies of the uterus were present in 9 cases. One instance of uterus unicornis, 2 of uterus bicornis unicollis and 6 of uterus arcuatus. In one of the patients with uterus bicornis the hysterogram showed three membranes in one horn (Fig. 3). This woman underwent total hysterectomy 3 years after examination. Both macroscopic and microscopic examination failed to demonstrate any signs of adhesions.

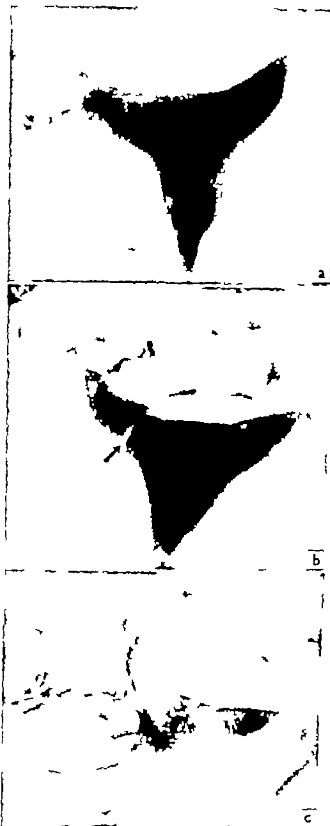


Fig. 6. Hyster grams from 1 case [illegible] examined three occasions. ( ) Prolifer[illegible] phase. (b) Tw[illegible] ears after a. Secret[illegible]y ph[illegible]. Upper membrane [illegible] right [illegible]terine cornu (arrow). ( ) Thr[illegible] e years [illegible] fte[illegible] b. Prol[illegible]fera[illegible] phase.

B. *Irregular membrane-like structures*

Case 1

A 26-year-old woman with a history of fi[illegible] spontaneous [illegible]bortions, in the seventh, third, fourth, fifth, and sixth months, respectively. Blunt curettage was performed after each abortion except the f[illegible]st. No infection followed any of the abortions. Hysterography 1 before the last pregnancy performed in the proliferative phase, was normal. Hysterography [illegible] taken [illegible] year after the last pregnancy in the secretory phase re[illegible]aled [illegible]xtensive irregular defects of identical form in all pictures (Fig. 7). They were interpreted as adhesions. During blunt curettage 4 [illegible]eeks later in the secretory phase no adhesions could be recognized. After another 4 months, hysterography 3 was made [illegible]th the patient in the early stage [illegible]f the secretory phase. At the beginning of this [illegible]xamination, irregular defects were seen. Their form, however, differed from that seen in the previous hysterography. Further they gradually disappeared during the [illegible]xamination, i.e. in about 10 min (Fig. 8 a–d). At hysteroscopy [illegible] days later no adhesions [illegible]ould be seen. Four [illegible]eeks later hysterogram 4 was taken, [illegible] the time of ovulation (Fig. 9). This examination showed a normal ca[illegible]ity without signs of adhesions.



Fig. 7. Case 1, hysterogram 1, showing extensive irregular defects in the uterine cavity. Secretory phase. (*a*) Postero-anterior projection taken at beginning of examination. (*b*) Left posterior oblique picture taken about 4 min after *a*. Note the similarity between certain portions of these defects and the membrane-like structures shown in Figs. 5 and 6.

Case

A 32-year-old woman with a history of four abortions, in the second, third, fourth, and third months of pregnancy respectively. Curettage was performed after the last three abortions. There was no infection after these interventions. Hysterography 1 after the first abortion, made in the secretory phase, was normal. Twelve months after the last abortion hysterography 2 was performed, again in the secretory phase, and revealed extensive irregular defects present in all pictures (Fig. 10). After a further 5 weeks, when the patient was in the proliferative phase, the uterine cavity was inspected by hysteroscopy and found to be normal. Two months later the patient conceived. The pregnancy and delivery were normal.

The incidence at Karolinska Sjukhuset of defects interpreted as pathognomonic of adhesions in the uterine cavity is rather low. In a series of 6 000 hysterograms with various pathological findings, made between 1948 and 1968, we found 21 cases, including the two described here. This corresponds to 0.35%. The existence of ad-

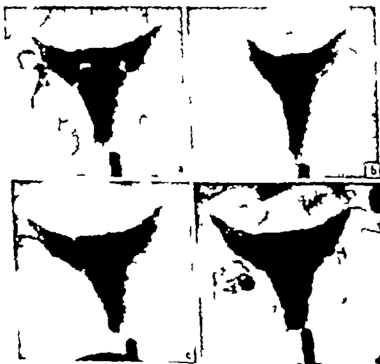


Fig. 8. Case 1, hysterogram 3 taken 5 months after hysterogram 2. Early secretory phase. All pictures taken during the same examination. (*a*) Extensive irregular defects, differing in form from those seen in Fig. 7. (*b*) One minute after *a*. The defects are smaller. (*c*) Two minutes after. The defects in the left uterine cornu have disappeared. The defects in the right uterine cornu assumed a form indistinguishable from that of membrane-like structures (see Figs. 5 and 6). (*d*) Three minutes after: all defects have disappeared.

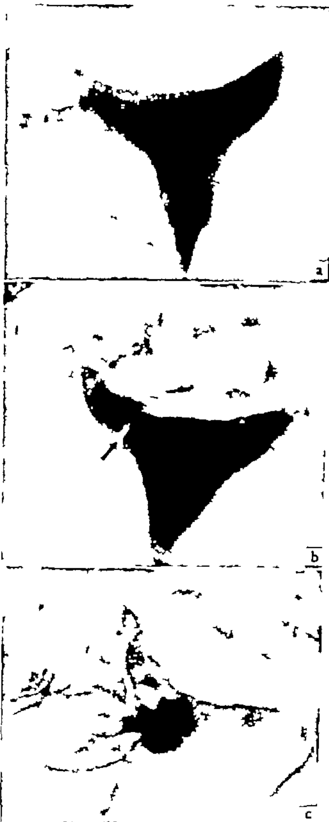


Fig 6. Hysterograms from 1 case examined three occasions. ( ) Proliferative phase. (*b*) Two years after *a*. Secretory phase. Upper membrane in right uterine cornu (arrow). ( ) Three years after *b*. Proliferative phase

ter-like structures in the isthmus were present. In these 15 cases "tubal sphincters" were seen on 3 occasions. Therefore there seemed to be a good correlation between the presence of "tubal sphincters" and uterine membranes.

Two or more hysterographies were performed in 9 cases. In 6 of these upper membranes were seen on the first examination but not on the second. Two of these are particularly interesting in that only 2 weeks elapsed between the first and the second examination performed in the secretory and proliferative phase, respectively with no intervening surgery (Fig. 5). In 2 cases the membranes were seen on both occasions. One patient, who was examined three times, exhibited membranes on the second occasion only (Fig. 6).

No membranes were seen in 10 of the 36 hysterograms. It is interesting to note that 7 of these were performed during the proliferative phase. Anomalies of the uterus were present in 9 cases: One instance of uterus unicornis, 2 of uterus bicornis unicollis and 6 of uterus arcuatus. In one of the patients with uterus bicornis the hysterogram showed three membranes in one horn (Fig. 3). This woman underwent total hysterectomy 3 years after examination. Both macroscopic and microscopic examination failed to demonstrate any signs of adhesions.

B *Irregular membrane-like structures*

Case 1

A 26-year-old woman with history of five spontaneous abortions, in the seventh, third, fourth, fifth, and sixth months, respectively. Blunt curettage was performed after each abortion except the first. No infection followed any of the abortions. Hysterography 1 before the last pregnancy performed in the proliferative phase was normal. Hysterography 2 taken year after the last pregnancy in the secretory phase revealed extensive irregular defects of identical form in all pictures (Fig. 7). They were interpreted as adhesions. During blunt curettage 4 weeks later in the secretory phase, no adhesions could be recognized. After another 4 months, hysterography 3 was made with the patient in the early stage of the secretory phase. At the beginning of this examination, irregular defects were seen. Their form, however differed from that seen in the previous hysterography. Further they gradually disappeared during the examination, i.e. in about 10 min (Fig. 8 *a*–*d*). At hysteroscopy days later no adhesions could be seen. Four weeks later hysterogram 4 was taken, at the time of ovulation (Fig. 9). This examination showed normal cavity without signs of adhesions.

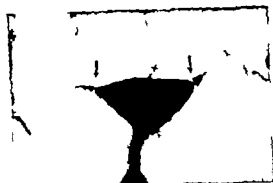


Fig. 11. Hysterogram showing the "tubal sphincters" (arrow).

ing the course of the examination contradict this hypothesis and favour the idea that the membranes are due to local uterine contractions. Further evidence of this is the circumstance that all histological examinations referred to in the literature have failed to demonstrate any mucosal folds which correspond to these membranes.

In some respects these structures resemble the "tubal sphincters" situated at the junction of the uterine cavity and the intramural portion of the tubes (Fig. 11). They also exhibit certain similarities to the sphincter-like structures sometimes seen at the anatomical internal os (AIO), that is at the transition between the isthmus and the corpus, as well as at the histological internal os (HIO), that is at the transition between the cervix and the isthmus (Fig. 12).

A most convincing item of evidence supporting the view that the "tubal sphincters" are of muscular origin appears to be the cineradiographic examinations of Proux et al. (1961) and Leszczynsky et al. (1961).

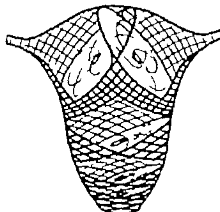


Fig. 13. Schematic representation of the arrangement of the principal muscle fibres in the human uterus (Goertler Morphol. Jahrbuch, 1930).

Further it is well known that a large part of the uterus, such as a uterine cornu, is able to contract but, apart from the "tubal sphincters" the only description of contractions of a few muscular loops alone is that by Rozin (1965), who presents an illustration of a membrane identical to those we have encountered. Rozin interprets this structure as a "segmental contraction". Further evidence is found in the striking agreement between the arrangement of the circular layer of uterine muscle and that of the membranes (Fig. 13).

Since the origin of the membrane-like contractions might well be the same as that of the tubal sphincters, it might be of value to study the simultaneous occurrence of these two phenomena. We found a correlation in 27 of the 36 examinations in our series. Such a pronounced concomitance might indicate that the structures have the same origin.



Fig. 12. Hysterogram. (*a*) shows sphincter-like structure at the transition between the isthmus and the cavity (anatomical internal os, arrow). (*b*) The same structure (upper arrow) and another membrane at the transition between the cervix and the isthmus (histological internal os, lower arrow).



Fig 9 Case 1 hysterogram 4 taken 4 weeks after hysterogram 3 at the time of ovulation. No defects in the uterine cavity

hesions was confirmed in 10 of these cases as follows: hysterectomy (1 case), hysterotomy (1 case), hysteroscopy (1 case), removing of adhesions by curettage (3 cases) Caesarian section (1 case) and probe exploration (3 cases). In the 9 cases remaining after exclusion of the two under discussion, the X-ray findings were not confirmed.

DISCUSSION

A *Regular membrane-like structures*

In the total series of hysterograms examined the incidence of membrane-like contractions was about one in 400 cases. Even with regard to the low incidence, the very small number of cases previously reported in the literature is remarkable in relation to the great number of hysterographies performed at many radiological departments. This might in part be because the technique used and especially the contrast medium used in many places is not very suitable for demonstrating fine structural details.

The phenomenon described by Asplund in 1957 as a stricture is identical to the structures we have encountered. The following circumstances strongly indicate that they are not adhesions.

(*a*) Repeated examinations show that they are inconstant. They have also been found to disappear during the course of a single examination.

(*b*) The form and site of the structures are almost identical from one case to another. This is in contrast to the irregularity of form and variation of site from one case to another which are typical of adhesions.

(*c*) The most common cause of adhesions is curettage performed post partum or after an abortion. However about half of our cases were nulliparous.

(*d*) One of our patients underwent hysterectomy Examination of the specimen failed to show any evidence of adhesions.

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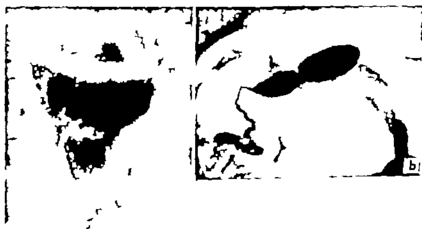


Fig 10 Case 2, hysterogram 2 Secretory phase. Extensive irregular defects, constant throughout examination. (*a*) Posteroanterior projection. Note the membrane-like defect in the right uterine cornu (*b*) Right posterior oblique projection taken during the same examination. Anteflexion of uterus provides cranial view of the fundal part, showing the membrane-like appearance of the defect in the right uterine cornu (compare Figs. 5 and 6).



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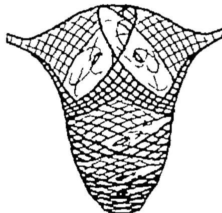


Fig. 13. Schematic representation of the arrangement of the principal muscle fibres in the human uterus (Goerttler, Morphol. Jahrbuch, 1930).

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In some respects these structures resemble the "tubal sphincters" situated at the junction of the uterine cavity and the intramural portion of the tubes (Fig. 11). They also exhibit certain similarities to the sphincter-like structures sometimes seen at the anatomical internal os (AIO), that is at the transition between the isthmus and the corpus, as well as at the histological internal os (HIO), that is at the transition between the cervix and the isthmus (Fig. 12).

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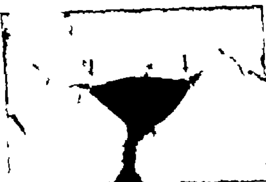


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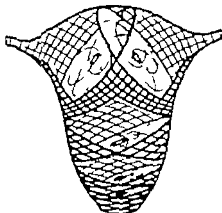


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Since the membranes are only 1–2 mm thick, and since they must include two mucosal layers, the suggestion that they also contain muscle might seem presumptuous. However in order to cover the muscle the mucosa must in all probability be considerably stretched and accordingly attenuated, thereby bringing about a reduction in the total thickness of the membrane

It is possible to distinguish the upper uterine contractions from the "tubal sphincters" and the lower ones from the structures at the AIO and HIO The following findings would exclude mistakes in this respect.

(*a*) In many cases of upper and lower contractions there was a simultaneous presence of "tubal sphincters" and structures at the AIO

(*b*) The distance between the "tubal sphincters" or the place corresponding to their site, and the contractions was in all instances more than 1 cm. The lower contractions were always situated well above the isthmus, and in the part of the cavity considerably wider than the isthmus. The average distance between the lower contractions and the AIO in our cases was 27 mm.

From a physiological point of view the study contributes some information about the contractile capacity of the myometrium and its relationship to the menstrual cycle. The regular membrane-like contractions were commonest in the secretory phase, during which they were found to be constant throughout the examination. They were less common in the proliferative phase, during which they were inconstant and found to disappear during examination. We do not know why these contractions were so often found in combination with anomalies of the uterus.

There is no evidence that the membrane-like contractions would lead to any disorders. Our series contains a large proportion of patients with infertility and recurrent abortion This, however is not remarkable in consideration of the high incidence of these disorders in patients referred for hysterosalpingography None of our patients suffered from dysmenorrhea.

B *Irregular membrane-like structures*

In most accounts of intrauterine adhesions, the hysterographic findings, i.e. of irregular defects in the uterine cavity have been regarded as full evidence of the presence of adhesions (Netter et al 1956 Asherman 1957 Bergman, 1961) Although, in some instances, the adhesions have actually been demonstrated at operation or otherwise, no confirmation of the X ray picture has been put forward in the majority of cases. This is understandable, as there cannot reasonably have been any circumstances, clinical or radiological, to raise doubts about the supposed organic origin of the defects.

Zondek's & Rozin's report (1964) of 4 cases of intrauterine filling defects is unequivocal evidence that these defects are not adhesions but structures of functional origin representing contractions. These patients were referred to hospital because of habitual abortion, and after denervation of the uterus or incision of the myometrium the defects disappeared and all were able to follow pregnancy through to term. The authors conclude that defects of this kind may be due to contraction effects caused by neuromuscular changes.

Our 2 cases differ from those described by Zondek & Rozin in that the defects disappeared spontaneously However in the introduction to their article, Zondek & Rozin mention that they had "noted that defects may change in localization and form from one picture to the next, which raised the question as to whether defects are always organic in origin" This is in keeping with their spontaneous disappearance during the examination and it supports the view that these defects are functional structures.

It could be objected that the defects in our 2 cases were actually adhesions which were ruptured by increasing pressure during hysterography or by curettage The following points are evidence that this is not the case

In case 2 the defects were constant throughout hysterography 2, i.e even after maximum distension of the uterus. There was no intervention of any kind between this hysterography and hysteroscopy 5 weeks later If therefore the defects had been true adhesions, there is no reason why they should not have been evident at hysteroscopy as well.

In case 1 hysterography 2 had shown intrauterine defects, and the curettage 4 weeks later was performed with the purpose of verifying adhesions. However nothing but a normal cavity could be found, and the microscopic examination showed normal mucosa. Further it might b objected that this curettage ruptured the earlier adhesions and caused new adhesions, which would have

had time to develop until hysterography 3 i.e. the occasion when defects of different configuration were shown in the first picture, but disappeared during examination. The disappearance of the defects would then have been caused by pressure rise at the hysterography The following factors contradict such argument.

1 At the time of the first exposure of hysterography 3 the amount of contrast medium was about 8 ml. The additional amount injected was about 2 ml thus a ery small proportion of the total amount The smallness of this increase is also quite obvious from the pictures. Furthermore the tubes were patent, allowing contrast medium to escape from the uterus, thus preventing any sudden increase in pressure and volume. Finally no general anesthesia was given, the injection was always done with great care and the patient did not experience any pain.

2 Persistence of defects during a hysterographic examination has been used as an argument in favour of the existence of adhesions (Netter et al., 1956). If this argument is to be used, it could not b. applied to hysterography 3

3 Hysteroscopy was performed 2 days after hysterography 3 If the defects had been adhesions ruptured during hysterography hysteroscopy would ha revealed the sequelae f the ruptures, such as bleeding or cicatricial zones in the mucosa However nothing but a normal cavity and mucosa was seen

The irregular conf guration of the contractile structures in the cases described, as well as in those described by Zondek & Rozin, could not reasonably b: brought about by the sole action of the ircular inner layer of the myometrium. It would therefor be reasonable to assume that one or both of the other tw muscle layers participate in the contractions

A close study of case 1 shows that some defects, while disappearing, assume a form indistinguishable from that of the regular membrane-l k cont actions referred to above (Fig. 8) Returning to the first picture during the sam. hysterogr phy (Fig 8) it will b apparent that these thin membranes can be traced even there and that some part f the thicker irregular portions appear as fusions between different portions of the membr nes. This also applies to case 2 (Fig 10) Thus, although there is no definite evidence, it appe rs that the irregular membranes and the regular membrane-like structures are of the same nature.

Our cases, as well as those of Zondek & Rozin, show that the hysterographic picture alone cannot be used as proof of adhesions, as has been done before. In a series of 1 cases of extensive ir regular defects collected at Karolinska Sjukhuset, the presence of adhesions could be proved only in ten. We know that the defects of the 2 cases described are not adhesions. Regarding the re maining 9 cases, we do not know whether the defects were adhesions or contractions. Thus, if one encounters defects on hysterography and if they cannot b: shown to disappear during examination, it is necessary to follow up with a hysteroscopic examination or at least with repeat hysterographies in different phases of the menstrual cycle. It is most probable that some cases of adhesions described earlier are not adhesions. It would therefore appear that cases of contraction have been erroneously treated as adhesions. Furthermore, the good therapeutic results ascribed to certain methods would have to be revised.

REFERENCES

Asherman, J Int J Fertility 2 49 1957

Asplund, J The Uterine Cervix and Isthmus under Normal and Pathological Conditions, p 58. Acta Radiol Suppl 91 1952

Bergman, P Acta Obstet Gynec Scand 40 Suppl. 4 1961

Fernström, I & Edström, K T be published.

Jarcho, J Gynaecological Roentgenology Hoeber New York, 1931.

Leszczynska, S., Marzcuk, K & Poniatowska, T Sem Hop (Paris) 36 2667 1961

Netter A Musset, R Lambert, A. & Salomon, Y Am J Obst & Gynec 71 368 1956

Proux, Ch., Oury F & Nahum, H Annales de Radiologie 4 199 1961

Rozin, S Uterosalpingography in Gynecology pp 52 and 208 Charles C Thomas, Springfield, 1965

Zondek, B & Rozin, S Am J Obst & Gynec 88 123 1964

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HYDATIDIFORM MOLE, INVASIVE MOLE AND CHORIOCARCINOMA IN SWEDEN 1958–1965

N. Ringertz

From the Department of Pathology II (Head: N. Ringertz), Karolinska Institutet Stockholm, Sweden

Abstract. All cases of hydatidiform mole, invasive mole and choriocarcinoma reported to the Swedish Cancer Registry as first diagnosed during the years 1958 through 1965 have been analyzed. The series comprises 631 cases of hydatidiform mole not followed by malignancy, 13 cases of invasive mole, 10 of choriocarcinoma developing after hydatidiform mole and 14 of choriocarcinoma without proven preceding mole. The frequency calculated on the number of medically registered pregnancies (births and abortions) is 1: 1 560 for hydatidiform mole, 1: 77 000 for invasive mole and 1: 41 000 for choriocarcinoma (Table III). The age specific rates per pregnancy rise significantly after the age of 40 both for benign mole and the malignant conditions (Table IV). The 37 cases of invasive mole and choriocarcinoma have been analyzed as to parity, clinical course, metastases, and survival time (Tables V–IX). It is of considerable prognostic value to separate invasive mole and choriocarcinoma (following the definitions of Hertig and Novak). In this series (histologically revised by the author) all 13 patients with invasive mole (all of them treated with hysterectomy) were living and free from symptoms 2–9 years after the mole delivery. In the group, choriocarcinoma after mole 5 patients are living symptom-free more than 9 years after the mole delivery but 5 died from the tumour within 5 years. The group, choriocarcinoma without preceding mole proved most malignant; only 2 out of 14 survived 6–7 years. Of the 9 patients in this group with choriocarcinoma after term or near term pregnancy 8 died within 18 months. The evaluation of chorionepithelial atypia in mole curettings (3 step grading of Hertig) was not shown to be of prognostic value in this study. Regressing lung metastases were shown in 3 out of 13 patients with invasive mole. Five patients dead by metastases of choriocarcinoma were shown to have normal uterus at autopsy.

The conditions connected with abnormal proliferation of chorionic epithelium, i.e. hydatidiform mole, invasive mole and choriocarcinoma are *rare* in European countries and the USA. There are indications that they are more common in certain other parts of the world, especially in the Far East—among Chinese and Japanese—and in at least one African country—Nigeria.

Table I gives some figures taken from the UICC-publication *Cancer Incidence in Five Continents*" (1966) where data reported by Cancer Registries from different parts of the world have been collected. It is seen that the figures for the site 173 (defined as including malignant chorionepithelioma) are decidedly higher in the Chinese population of Singapore, in the Miyagi district in Japan, and in the Ibadan district in Nigeria than in the Scandinavian countries, in Yugoslavia and in New York State.

A comparison of this kind is invalidated in many respects, however. It is possible that in some of the regions tabulated here a few ill-defined uterine malignancies, beside the chorionic, are reported under site 173 (this is not the case for the Scandinavian countries); furthermore, in none of the regions is the incidence of invasive mole defined. Finally the incidences are computed on whole female population, and the number of pregnancies in the various populations is not taken into account.

The aim of this paper is to give a review of the occurrence of hydatidiform mole, invasive mole and choriocarcinoma in Sweden during the period 1958 through 1965 and to *analyze the* frequency of these conditions, not only in relation to the female population, but also in relation to the number of births and known abortions during the period. The material has been collected on the basis of reports received by the Swedish Cancer Registry (reporting of cases of both hydatidiform

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Abstract. All cases of hydatidiform mole, invasive mole and choriocarcinoma reported to the Swedish Cancer Registry as first diagnosed during the years 1958 through 1965 have been analyzed. The series comprises 631 cases of hydatidiform mole not followed by malignancy 13 cases of invasive mole, 10 of choriocarcinoma developing after hydatidiform mole and 14 of choriocarcinoma without proven preceding mole. The frequency calculated on the number of medically registered pregnancies (births and abortions) is 1 1 560 for hydatidiform mole, 1 77 000 for invasive mole and 1 41 000 for choriocarcinoma (Table III) The age specific rates per pregnancy rise significantly after the age of 40 both for benign mole and the malignant conditions (Table IV). The 37 cases of invasive mole and choriocarcinoma have been analyzed as to parity clinical course, metastasis, and survival time (Tables V–IX) It is of considerable prognostic value to separate invasive mole and choriocarcinoma (following the definitions of Hertig and Novak). In this series (histologically revised by the author) all 13 patients with invasive mole (all of them treated with hysterectomy) were living and free from symptoms 2–9 years after the mole delivery In the group choriocarcinoma after mole 5 patients are living symptom-free more than 9 years after the mole delivery but 5 died from the tumour within 5 years The group, choriocarcinoma without preceding mole proved most malignant; only 2 out of 14 survived 6–7 years Of the 9 patients in this group with choriocarcinoma after term or near term pregnancy 8 died within 16 months The evaluation of chorionepithelial atypia in mole curettages (3 step grading of Hertig) was not shown to be of prognostic value in this study Regressing lung metastases were shown in 3 out of 13 patients with invasive mole Five patients dead by metastases of choriocarcinoma were shown to have normal uterus at autopsy

The conditions connected with abnormal proliferation of chorionic epithelium, i.e. hydatidiform mole, invasive mole and choriocarcinoma are rare in European countries and the USA. There are indications that they are more common in certain other parts of the world, especially in the Far East—among Chinese and Japanese—and in at least one African country—Nigeria.

Table I gives some figures taken from the UICC-publication *Cancer Incidence in Five Continents*" (1966) where data reported by Cancer Registries from different parts of the world have been collected. It is seen that the figures for the site 173 (defined as including malignant chorionepithelioma) are decidedly higher in the Chinese population of Singapore, in the Miyagi district in Japan, and in the Ibadan district in Nigeria than in the Scandinavian countries, in Yugoslavia and in New York State

A comparison of this kind is invalidated in many respects, however It is possible that in some of the regions tabulated here a few ill-defined uterine malignancies, beside the chorionic, are reported under site 173 (this is not the case for the Scandinavian countries) furthermore, in none of the regions is the incidence of invasive mole defined. Finally the incidences are computed on a whole female population, and the number of pregnancies in the various populations is not taken into account.

The aim of this paper is to give a review of the occurrence of hydatidiform mole, invasive mole and choriocarcinoma in Sweden during the period 1958 through 1965 and to analyze the frequency of these conditions, not only in relation to the female population, but also in relation to the number of births and known abortions during the period. The material has been collected on the basis of reports received by the Swedish Cancer Registry (reporting of cases of both hydatidiform

Table I. *Mean annual age specific incidences under site 173 per 100 000 female population. Figures fr[illegible] various Cancer Registries reproduced from the UICC publication "Cancer Incidence in Five Contin[illegible]*

Age groups	15–19	20–24	25–29	30–34	35–39	40–44	45–49	50–5[illegible]
Singapore, Chinese 1950–61	0.2	2.5	2.7	3.1	4.2	2.8	3.2	[illegible]
Japan Miyagi 1959–60	0	[illegible].6	4.0	5.6	3.3	2.0	7.7	1.3
Nigeria, Ibadan 1960–62	2.1	3.6	2.4	3.3	8.9	9.3	0	0
Sweden 1959–61	0	0	0.8	1.0	0.7	0	0.1	0.3
Norway 1959–61	0	0	1.4	0.3	0.5	0.5	0.3	0
Denmark 1953–57	0.1	0.3	0.1	0.4	0.2	0	0.3	[illegible]
Yugoslavia 1956–60	0	0.6	0.6	0	0.4	0.5	1.5	0.4
New York State 1959–61	0	0.3	0.5	0.2	0.2	0.3	0.1	0.3

mole and chorionepithelioma" is compulsory). The heading "chorionepithelioma" includes both invasive mole and choriocarcinoma. The author has personally examined the slides of the cases of "chorionepithelioma" in order to be able (1) to exclude erroneous diagnosis (especially "syncytial endo-myo-metritis" which is easy to mistake for choriocarcinoma), and (2) to distinguish between invasive mole and choriocarcinoma. The slides of the cases of hydatidiform mole not followed by malignancy have not been reexamined. The clinical records (including necropsy records) have also been reviewed in the cases of invasive mole and choriocarcinoma in order to be able to analyze several circumstances of biological and pathological interest in these cases as well as the outcome of the disease.

During the period 1958 through 1965 654 cases of hydatidiform mole and 40 cases of "chorionepithelioma" were reported to the Registry (Ringertz et al., 1960–1969). Of the hydatidiform moles 13 were later found to be invasive and in 10 cases the mole was followed by choriocarcinoma. The review of the slides of the 40 cases reported to the Registry as chorionepithelioma revealed a completely false diagnosis (metastasizing intestinal adenocarcinoma) in 1 case, and in 2 cases the diagnosis was revised to "syncytial endometritis". In both the latter cases the diagnosis was founded on curettage only, hysterectomy was not performed and the patients later had normal pregnancies. The histological analysis revealed out of the remaining 37 cases, 13 were invasive moles and 24 were true choriocarcinomas. Following the definition of Novak (1968) and also of Hertig (1956) invasive mole was diagnosed when molar villous structures were observed in myometrial vessels. In addition there may be considerable tissue invasion by chorionic cells, but as long as molar villi are found as a part of the invasive tissue the case has been classified as invasive mole and not as choriocarcinoma. The latter diagnosis was reserved for cases showing clearly destructive myometrial invasion by chorionic elements but absence of villous structures. In some cases the diagnosis of choriocarcinoma was founded on the findings in metastatic tissue only. In these cases also the absence of chorionic villous structures was decisive.

In 10 of the 24 cases of choriocarcinoma the malignant lesion was preceded by delivery of a mole. Thus, in Sweden the following numbers of verified cases have been reported during the period 1958–1965.

Table II. *The numerical age distribution of the cases of hydatidiform mole, invasive mole and choriocarcinoma in Sweden 1958–1965*

Age groups	15–19	20–24	25–29	30–34	35–39	40–44	45–49	50–54	Total	Mean age
Hydatidiform mole	70	175	169	98	56	14	16	13	631	28.5
Invasive mole	1	3	1		4		1	1	13	32.9
Choriocarcinoma preced. by mole		2	2		2		3	1	10	37.0
Choriocarcinoma not preced. by mole			5	4	2	1	1	1	14	34.6
All choriocarcinoma		2	7	4	4	1	4	2	24	35.6

Table III *Annual rates in Sweden 1958–1965*

Average annual rates	Benign mole	Invasive mole	Chorio-carcinoma	Total of inv mole and chor ca
Per 100 000 female population	44	0 054	0 079	0.133
Per 100 000 fem. pop. ages 15–54	3.93	0 080	0 147	0.227
Per 1 000 registered pregnancies (births and abortions)	0 64 (1 1 560)	0 013 (1 77 000)	0 024 (1 41 700)	0 037 (1 27 000)

Hydatidiform mole not followed by malignancy	631
Invasive mole	13
Choriocarcinoma preceded by mole	10
Choriocarcinoma not preceded by mole	14

Table II shows the age distribution and average age of these patients. The age is given as at the delivery of the mole or at the end of the pregnancy followed by malignancy

The frequency of benign mole invasive mole and choriocarcinoma in relation to the female population and the number of medically gistered pregnancies

The figures are given in Table III. The total rate of abnormal chorionic proliferation is 2.77 per 100 000 of the whole female population and 4 16 per 100 000 in the age groups 15–54 years. The corresponding rates for hydatidiform mole are 2.64 and 3 93 respectively and for malignant chorionic proliferation 0.13 and 0.23 per 100 000 population. The figures of real biological interest would be the proportion of pregnancies in which these bnormalities occur especially when international comparisons are made However this is impossible, even in countries with well developed statistical registration. First, there is an incalculable number of early abortions never treated medically and probably not even recognized as abortion by the women. Second, many abortions in the 3rd and 4th month of gestation no doubt occur without any medical treatment. The best base figure it is possible to give for Sweden is the total number of births (including still-births and prematures), medically treated spontaneous abortions, and "legally" performed abortions. During the years 1958–1965 the number of births was 882 147 (multiple births counter as one) and the number of medically registered abortions was 117 423 The total, 1 009 570 pregnancies, is the base figure on which the average annual rates in the 3rd line in Table III is computed (*Public Health in Sweden, Ann. Rep s 1958–1965*) The total rate of abnormal chorionic proliferation is 0.68 per thousand known pregnancies (or 1 1 470) and the rate of malignant proliferation is 0 037 per thousand (or 1 27 000). The ratio benign mole/malignancy was 17.3 1 Of the 654 cases of hydatidiform mole reported in 1958–1965 13 were later found to be invasive and 10 were followed by choriocarcinoma, i.e. malignancy developed in 3.5% (or once in about 28 cases).

The frequency f benign mol invasive mole and horiocarcinoma in relation to age

It is impossible to find statistics on the ge distribution of all medically treated abortions in Sweden, so in this comparison the rates are computed

Table IV *The specific age incidence per 1 000 births (multiple births counted as one) for hydatidiform mole invasive mole and choriocarcinoma in S eden 1958–1965*

Age groups	20	20–24	25–29	30–34	35–39	40	All ages
Number of mothers (thousands)	87	258	260	164	85	29	883
Benign moles per 1000 mothers	0 805	0 678	0 650	0 598	0 659	2 172	0.715
Invasive moles per 1000 mothers	0 011	0 011	0 004	0 012	0 047	0 069	0 015
Choriocarcinoma per 1000 mothers	—	0 008	0 027	0 024	0 047	0 240	0 027
Inv mole chor ca per 1000 mothers	0 011	0 019	0 031	0 036	0 094	0 309	0 042
Proportion ben mole to malignancy	73 1	36 1	21 1	17 1	7 1	7 1	17 1

Table V *Data on 13 cases of invasive mole*

Age at delivery	See Table II					
Gravidity includi g molar pregnancy	1st 5	2nd 3	3rd 2	4th 2	5th 1	pregnancy cases
Gestation period (months)	1st 5	2nd 3	3rd 2	4th 2	5th 1	month cases
Time lapse from mole-delivery to hysterectomy	0 3[a]	< 30 2	30–60 4		75–195 4	days cases
Survival in years (no patient dead)	2 3 1	3–4 1	4–5 1	5–6 1	8–9 3	> 9 6

In this case one earlier benign mole

[a] Immediate hysterectomy following diagnosis of mole.

on "mothers" (still births and prematures included, multiple births counted as one) The figures are given in Table IV It is seen that for benign mole there is little variation of the rates up to the age of 39 but a significant rise after the age of 40 As to the malignant conditions (5th line in Table IV) there is also a progressive rise in relation to age, with a very marked increase after the age of 40 As a consequence the ratio benign mole/malignancy decreases steadily up to the age of 35 (last line in Table IV)

Some clinical data on the cases of invasive mole and choriocarcinoma

The material has been devided into groups (1) invasive mole (2) choriocarcinoma developed from mole (3) choriocarcinoma after full term or nearly full term pregnancy and (4) choriocarcinoma after abortion or tubal pregnancy The data are summarized in Tables V–VIII

Parity In Table IX the parity of the women with chorionic malignancy is compared with the yearly average among all mothers (definition see above) in Sweden during the years 1958–1965. It is seen that overall lower parities predominate. In the group of moles with invasiveness or followed by choriocarcinoma the distribution between parities is fairly even and in cases of choriocarcinoma without known preceding mole higher parities predominate. This illustrates a rising risk of chorionic malignancy with multiparity —about two times greater risk for choriocarcinoma witholut mole in women with two or more preceding pregnancies than for the primipara. Among the choriocarcinomas the malignant pregnancy was the 7th in 2 cases, the 8th in 1 case, and the 13th in 1 case.

Table VI *Data on 10 cases of choriocarcinoma following hydatidiform mole*

Age t delivery	See T ble II								
Gravidity including molar pregnancy	1st 2	2nd 5	3rd —	4th —	5th —	6th 1	7th 1	8th 1	pregnancy cases
Gestation period (months)	1st —	2nd 1	3rd 3	4th 4	5th 2				month cases
Time lapse from mole delivery to hysterectomy	0 3[a]	30 2	40 1	75 1	120 1	160 1	240 1		days cases
Deaths Survival in years	< 2 1	2 3 2	3–4 1	4–5 1					cases
Living after more than 9 years 5 cases									

I two f these cases no hysterectomy both dead with metastases but without sign of tumour in the uterus on autopsy In the 3rd case hysterectomy was performed immediately on diagnosis of mole. The patient died later with metastases of choriocarcinoma.

[b] No choriocarcinoma found in uterus but dead with metastasis.

Table VII. *Data on 9 cases of choriocarcinoma after term or near term delivery*

Age at delivery	25–29		30–34	35–39	40–44	years
	3		4	1	1	cases
Gravidity	1st		2nd	3rd	4th	
	2		4	1	2	cases
Time lapse from delivery to hysterectomy	0	< 60	60–120	180–190	> 360	days
	2[a]	1	3	2	1	cases
Deaths	< 5		6–12	12–18		months
Survival in months	2		4	2		cases
Living after more than 6 years: 1 case						

[a] No hysterectomy, both patients later dead with metastasis.

The course of the development of malignancy after hydatidiform mole

Of the 23 patients developing malignancy connected with hydatidiform mole 4 were subjected to hysterectomy directly after the diagnosis of the mole. In 3 of these cases the mole was found to be invasive. In the fourth case no invasiveness was detected in the specimen and hormone and histaminase titres returned to normal, but 2 years later metastases developed which killed the patient. The metastatic tissue was frankly choriocarcinomatous without villous structures. In another 2 cases hysterectomy was never performed. In both cases the hormone titres returned to normal rapidly after the mole delivery but later distant metastasis of frankly choriocarcinomatous character led to death. In both these cases the autopsy revealed a normal uterus. In 9 of the remaining 17 cases the hormonal and/or histaminase titres remained high after the mole delivery and hysterectomy was performed within 2 months. Six of these patients were found to have invasive mole and 3 choriocarcinoma. In another 5 cases the titres returned to normal rapidly after the mole delivery but later rose again and hysterectomy was performed after a delay of 75–195 days. Four of these were found to have invasive mole and one choriocarcinoma. Finally in 3 cases with choriocarcinoma with a delay before hysterectomy of 120, 160 and 40 days, respectively the preg-

Table VIII. *Data on five remaining cases of choriocarcinoma*

Case	Age	No. of the last pregnancy	Character of the last pregnancy	Subsequent course: Dead	Subsequent course: Living
1	37	4th[a]	Ab. mens 2		> 7 y
2	25	2nd[a]	Ab. mens 3	3 y 10 mo.	
3	33	7th	Ab. mens 4	5 y 6 mo.	
4	49	13th	Missed abortion	5 mo.	
5	23	1st	Tubal pregnancy	3 mo.	

[a] One earlier benign mole.

Table IX. *The parity of the patients with choriocarcinoma compared with the overall parity distribution in the population*

No. of pregnancy	Overall distribution (%)	Mole followed by malignancy (%)	Choriocarcinoma without mole (%)
First	41.3	30	22
Second	31.9	35	36
Third or subsequent	26.8	35	43

Table V *Data on 13 cases of invasive mole*

Age at deli ery	See Table II					
Gravidity including molar pregnancy	1st 5	2nd 3	3rd 2	4th 2	5th 1	pregnancy cases
Gestation period (months)	1st 5	2nd 3	3rd 2	4th 2	5th 1	month cases
Time lapse from mole-deli ery to hysterectomy	0 3[b]	<30 2	30–60 4		75–195 4	day cases
Survival in years (no patient dead)	2–3 1	3–4 1	4–5 1	5–6 1	8–9 3	>9 6

In this case one earlier benign mole.
[b] Immediate hysterectomy following diagnosis of mole.

on "mothers" (still-births and prematures included, multiple births counted as one) The figures are given in Table IV It is seen that for benign mole there is little variation of the rates up to the age of 39 but a significant rise after the age of 40 As to the malignant conditions (5th line in Table IV) there is also a progressive rise in relation to age with a very marked increase after the age of 40 As a consequence the ratio benign mole/malignancy decreases steadily up to the age of 35 (last line in Table IV)

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Table VI *Data on 10 cases of choriocarcinoma following hydatidiform mole*

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Gestation period (months)	1st —	2nd 1	3rd 3	4th 4	5th 2				month cases
T me lapse from mole delivery t hysterectomy	0 3[a]	30 2	40 1	75 1	1[illegible]0 1	160 1	40 1		day cases
Deaths Survival in years	<2 1	2 3 2	3–4 1	4–5 1					cases
Living after more tha 9 years 5 cases									

I t o of these cases no hysterectomy both dead w th metastasis but without signs of tumour i the uterus on autopsy I the 3rd case hysterectomy was performed mmediately on diagnosis of mole. The patient died later w th metastasis of choriocarcinoma.
[b] No choriocarcinoma found in terus but dead with metastasis.

metrial hyperplasia was diagnosed. A rather rapidly growing adnexal mass was palpated and on laparotomy a grapefruit-sized tumour destroying the right adnexa and invading the peritoneum was found. The tumour could not be removed completely. Immediately after the operation the FSH titre was 200 000–500 000, and histopathology revealed choriocarcinoma. The patient died 3 months after the operation with a massive tumour infiltration in the pelvis, and retroperitoneal, hepatic, and pulmonary metastases. At autopsy the uterine mucosa was normal.

Metastasis

Roentgenologically regressing lung metastases with invasive mole were observed in 3 cases. The metastases were revealed at the time of the molar abortion. They regressed in 1 case within 2 months (roentgen therapy) and in 2 cases within 7 months (no therapy and Sendoxan therapy respectively).

Lung metastasis of choriocarcinoma was noted in 13 of the 24 cases (54%). One of these patients had roentgenologically confirmed metastases which regressed following methotrexate therapy. Hysterectomy was performed and the patient is alive more than 6 years later. Two patients had roentgenologically confirmed lung metastases and died but autopsy was not performed, while in 10 cases the metastases were confirmed at autopsy. In another 4 patients no lung metastases were shown before death but no autopsy was performed. In only one out of 11 patients submitted to autopsy were lung metastases absent. Thus, out of 17 patients dying from choriocarcinoma, lung metastases were shown in 12 (i.e. 70%), and may possibly have been present in another 4 cases not submitted to autopsy.

Vaginal metastasis was only recorded in 2 patients in this series. In both cases the metastases were clinically revealed after hysterectomy had been performed. In one of these cases the choriocarcinoma developed after term delivery and in the other after nonmolar abortion. Among the cases in which autopsy was performed, no vaginal metastasis was recorded.

Other metastases were observed in 9 out of 11 choriocarcinoma cases subjected to autopsy. The organ distribution was: brain, 4 cases; spleen 3 cases, retroperitoneal nodes, 3 cases; kidney 2 cases; bones, 1 case; skeletal muscle, 1 case; and small intestine, 1 case.

Survival

As shown in Tables V–VIII, all the 13 patients with invasive mole are living symptom-free 2 to 9 years after the end of the molar pregnancy. Of the 24 patients with choriocarcinoma, 17 died within 5 1/2 years, and 7 are living symptom-free at least 6–9 years after the end of the malignancy producing pregnancy. Within this group, there is a striking difference between the tumours of molar and non-molar origin. In the former group 5 died within 5 years and 5 are living more than 9 years later. Of the 14 patients with non-molar choriocarcinoma, 12 died within 5 1/2 years and 2 are living at least 6–7 years later. The subgroup choriocarcinoma after term or near term pregnancy had an especially bad prognosis, here 8 of 9 patients died within 18 months after the delivery.

COMMENTS

As shown in Table III the incidence of hydatidiform mole in Sweden does not exceed one in 1 560 recorded pregnancies and the rates for invasive mole and choriocarcinoma are very low: one invasive mole in 77 000 and one choriocarcinoma in 41 700 recorded pregnancies. Some of these figures are in reasonable agreement with the estimated figures of Hertig (1956) in the population of the USA: one hydatidiform mole in 2 000 and one choriocarcinoma in 40 000 pregnancies. Novak *et al.* (1968) give the figure one in 2 500 pregnancies for hydatidiform mole.

An analysis of the incidence of hydatidiform mole and chorioepithelial malignancies in different age groups (Table IV) shows a slight but continual increasing incidence with age up to 35 and after that age a marked increase in incidence. The risk of choriocarcinoma also increased with parity (Table IX). *Possibly this is only another expression of the age factor.* It is of interest to note that among the 73 recorded pregnancies preceding the index pregnancy 3 were hydatidiform moles, which gives one hydatidiform mole in about 24 pregnancies. This figure is 65 times the expected (1 : 1 560) and may indicate that an individual factor is of importance for chorioepithelial growth disturbance.

In the Swedish material choriocarcinoma developed after hydatidiform mole in 42%, after abortion (including tubal pregnancy) in 21%, and after term, or near term, pregnancy in 37%. The corresponding figures given by Hertig (1956) are

nancy tests were continuously positive after the mole delivery In 2 of these cases the uterus was found to be normal and the titres were explained by the presence of distant metastases. In the 3rd case the uterus contained choriocarcinoma. In spite of the long delay before hysterectomy this patient is still alive after more than 9 years.

The development of choriocarcinoma not preceded by diagnosed hydatidiform mole

In the 14 cases in this group the choriocarcinoma developed after term or near term delivery in 9 cases, after non-molar uterine abortion in 4 cases and after non-molar tubal pregnancy in 1 case. One case in the first sub-group is remarkable. The patient, aged 30 at the diagnosis of malignancy was delivered 2 years earlier of a stillborn boy weight 2 500 g and with multiple congenital malformations. The delivery preceding choriocarcinoma was of a stillborn girl, weight 1 750 g, also with multiple malformations. The placenta contained a walnut-sized focus of choriocarcinoma without molar structures. Multiple hazelnut-sized lung metastases were detected roentgenologically immediately after the delivery and a curettage revealed myometrial invasion of choriocarcinoma The patient succumbed after 4 1/ months in spite of intense methotrexate therapy This case proves that choriocarcinoma may develop during the pregnancy in a normal placenta and that the fetus may be retained in spite of the tumour development The majority of the patients in this subgroup with term or near term delivery had irregular post partum haemorhages for periods varying between 2 and 18 months, until curettage or rising hormonal titres indicated choriocarcinoma. After the diagnosis of choriocarcinoma was made, hysterectomy was performed immediately in all but 1 case This latter case showed lung metastases roentgenologically at the time of a positive curettage 3 weeks after delivery and following regression of the lung metastases under methothexate therapy hysterectomy was performed 3 months after delivery This patient is the only one in this group who recovered she is symptom free more than 6 years after the delivery Two of the patients in this sub-group were delivered by Caesarian section.

The 4 cases of choriocarcinoma following non-molar uterine abortion showed a rather varying and in some cases obscure course of the tumour developement. The data on these patients are briefly as follows (see also Table VIII):

1 Age 37 three earlier pregnancies, one of which 7 years earlier was a hydatidiform mole. Non-molar abortion occurred in the 3rd month and curettage revealed an atypical chorioepithelial proliferation. Two months later a pregnancy test was positive and the uterus was removed, showing choriocarcinoma. *The patient is living after more than 7 years.*

2 Age 25 one earlier pregnancy which was a hydatidiform mole years previously In her second pregnancy abortion, which was non-molar occurred in the 2nd month. *Seventeen months later a parametrial mass was* palpated and hormonal titres were suspicious of pregnancy On operation a walnut-sized brown and necrotic focus was found in the parametrium near the uterus. Since histopathology only revealed haemorrhage and necrosis, *no hysterectomy was performed. Six months later* she had signs of lung metastases and soon succumbed. The autopsy revealed choriocarcinoma in the uterus and multiple distant metastases.

3 Age 51 five earlier pregnancies. In 1957 she had a *histologically confirmed non-molar abortion in the 5th* month of pregnancy The uterus was myomatous. In the following years she had rather severe irregular haemorrhage and more than 4 years after the abortion (at the age of 55) hysterectomy was performed chiefly because *of the myomas. The only suspicious finding* was a curettage showing an endometrium with stromal decidual reaction and atrophic glands. In the myomatous uterus an intramural, walnut-sized choriocarcinoma was found. She soon developed vaginal metastasis and died 1 year after *the hysterectomy* with clinical signs of cerebral metastases. In this case it is of course possible that a later unrecognized abortion was the source f the malignancy

4 Age 49 twelve earlier pregnancies (one of which tubal). She had her last normal menstruation on Nov 1, 1959 During the following 6 months she had several irregular haemorrhages and in June 1960 the uterus was enlarged to the size of a fetal-head and a pregnancy test was positive. At the end of July (9 months after the last normal menstruation) she was delivered of a necrotic mass. Histologically neither villi, molar structures, nor choriocarcinoma were detected in this mass As haemorrhages persisted the uterus was removed 1 month later and the specimen contained *hazelnut-sized polypoid* choriocarcinoma invading the myometrium. The patient died with distant metastasis 4 / years fter the abortion. In spite of the negative histological examination, it is possible that the delivered mass was a totally necrotic *hydatidiform mole* it is also possible that it was necrotic choriocarcinomatous tissue. Considering lacking evidence of a mole the case has been included in the present subgroup of choriocarcinoma.

In the last case *in the choriocarcinoma group* the tumour is believed to have arisen from a tubal pregnancy The patient, aged _5 had no earlier pr[illegible] In the preceding 5 years she had irr

patients are symptom-free 6–9 years after the end of the malignancy-producing pregnancy. In the 13 cases which, after the author's revision of the slides, were classed as invasive mole, the original PAD on the hysterectomy specimen was choriocarcinoma in 8 cases—in spite of the fact that the presence of molar villi was mentioned in the histological description in several cases. The results of the follow up stress the importance of separating invasive mole from choriocarcinoma. Although the invasive mole may give rise to regressing lung metastases it rarely if ever causes death if the uterus is removed. Though generally included in the group of chorionic malignancy and referred to as such in this paper the invasive mole is in fact biologically benign lesion. However it is not possible to exclude, that an invasive mole left in the uterus for an extended period of time may change its character into choriocarcinoma. In such cases the malignant cell proliferation is likely to destroy the remainder of the molar villi. No histologically examined distant metastasis after hydatidiform mole in this series revealed any rests of molar villous structures.

Hertig & Sheldon (1956) stress that the degree of epithelial atypia found in the delivered mole is correlated to the later development of invasive ness or choriocarcinoma. The findings in this material do not confirm this view. It includes 20 cases of delivered mole (cases not primarily treated by hysterectomy) where invasive mole or choriocarcinoma was later diagnosed. When the mole picture in these cases was classed according to Hertig 3 step grading of atypia, only 5 came into grade 3 (apparently malignant), 3 corresponded to grade 2 (potentially malignant), while 12 belonged to grade 1 (apparently benign). This material also demonstrates a difference in prognosis between the group of choriocarcinoma preceded by mole and the group without proven preceding mole. In the former group 5 out of 10 patients are alive more than 9 years after the mole, while in the latter only 2 out of 14 are living after 6 or 7 years. The group choriocarcinoma after term or near term delivery proved especially malignant (9 of 10 patients dead within 18 months). In most of these cases it is probable that the choriocarcinoma developed during the pregnancy and it is possible that the retention of the pregnancy until term or near term is factor promoting the malignant course.

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REFERENCES

Acosta Sison, H. Obst Gynecol *10* 165 1957
Arlen, R. E. & Bertoli, F. Obst Gynecol *13* 737 1959
Brewer, J. J. & Gerber A. O. Obst Gynecol 94 692, 1966.
"Cancer Incidence in Five Continents. U.I.C.C. Report. Springer 1966
Chan, D. P. C. & Fang, L. S. C. J Obst Gy Brit C lth *71* 192, 1964.
Hertig, A. T. & Mansell, H. Hydatidiform Mole and Choriocarcinoma, A.F.I.P.'s Atlas of Tumor Pathology Female Sex Organs, Part 1 Washington D.C. 1956.
McRae, D. J. J Obst Gynecol Brit Emp 58 373, 1951.
Novak, E. R. & Woodruff, J. Gyn and Obstetr Pathology 6th edn, Saunders, 1968
Park, W. W. & Lees, J. C. Arch Path 49 205 1950.
Public Health in Sweden (Allmän Hälso- och Sjukvård) 1958, Official Statistics of Sweden 1960, Annual Rep of the National Bord of Health, pp. 62–69
— 1959 Off. Stat. 1961, pp 66–72.
— 1960, Off Stat. 1962, pp. 97 105
1961, Off Stat. 1963, pp 91 98
— 1962, Off. Stat. 1964 pp 99–106.
— 1963, Off. Stat. 1965 pp 97–104
— 1964, Off Stat. 1966, pp. 90–97
— 1965 Off Stat 1967 pp 97–104
Ringertz, N. Sjöström, A. Ericsson, J. & Olander, B. Cancer Incidence in Sweden 1958. Stockholm, 1960.
Ringertz, N. Sjöström, A. Törnberg, B. & Swenson, D. Cancer Incidence in Sweden 1959 Stockholm, 1962.
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Ringertz, N. Sjöström, A. Ericsson, J. & Swenson, D. Cancer Incidence in Sweden 1961 Stockholm, 1965.
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Even in such a comparatively small series of chorionic malignancy as the present a very variable pattern in the clinical course is demonstrated In the group associated with hydatidiform mole, the mole was proved to be invasive already at the time of delivery in 3 out of 23 cases, and in 9 cases persisting bleeding and raised hormone titres led to hysterectomy within 2 months after the mole delivery with detection of invasive mole in 6 and choriocarcinoma in 3 cases. In 5 cases the titres returned to normal after the delivery but rose again after 3–8 months and a delayed hysterectomy revealed invasive mole in 4 and choriocarcinoma in 1 case. It is of interest that none of the 4 cases of choriocarcinoma mentioned above had signs of distant metastasis and survived. In the remaining cases the persisting elevation of hormone titres were signs of distant metastasis of choriocarcinoma. In 4 of these cases the pathoanatomical examination of th uterus revealed no trace of tumour Thus, as shown in this material, a choriocarcinoma after hydatidiform mole may remain localized in the uterus for at least 6 months, or may immediately give rise to distant metastasis. It is known in the literature that metastases of choriocarcinoma may be present in patients with a normal uterus (Hertig et al., 1956 Acosta Sison, 1957 Arias et al., 1959 Chan et al., 1964) In such cases included in the present series, the recorded findings cannot elucidate the question whether a local choriocarcinoma had regressed, or if haematogenous spread of malignant chorionic cells had taken place without leaving any trace in the uterus.

It is known from the literature that choriocarcinoma may develop during the course of a pregnancy ending at term or near term (McRae 1951 Brewer et al., 1966) In 1 case in this series this was proven and in another one it was very probable (suspicious curettage 1 week post partum and roentgenologically evidenced lung metastases 2 weeks later). In the majority of the cases of post partum choriocarcinoma it cannot be decided whether the malignant proliferation started before or after delivery but in many cases the curettage gave suspected or clear pictures of choriocarcinoma 2 weeks – 2 months after the delivery and it is well possible that in these cases also the tumour was present at delivery In this group there was 1 case with the first malignancy diagnosis based on demonstration of metastases, with no tumour in the uterus at autopsy

In some of the cases of choriocarcinoma after abortion, it was difficult to evaluate the course of the malignancy-producing pregnancy Two women in the menopausal age (47 and 51 years, respectively) belong to this group In one of these cases the choriocarcinoma was mainly an accidental finding on removal of a myomatous uterus, and in the other case it cannot be excluded that the pregnancy was molar The proportion of choriocarcinoma after tubal pregnancy is stated to be 2.5% of all choriocarcinoma and it is apparently due to chance that 1 case is included in this series of 24 cases.

The lung is stated to be the most common site by far for distant metastasis in choriocarcinoma. It is also well known that with invasive mole roentgenologically diagnosed metastases may develop and later regress. This was observed in 3 out of 13 cases in this series, a lower frequency than that reported by e g. Wilson et al (1961) who found 8 such cases in their series of 20 It cannot be decided to what extent chemotherapy which was administered in two of the present cases, caused, or contributed to, the regression. Lung metastasis of choriocarcinoma occurred in 54 % of the whole series (including the surviving patients). Among the 17 deceased patients, the frequency was at least 70% but may possibly have been as high as 94% Vaginal metastasis, which in the literature is reported as second in frequency after lung (Park et al., 1950), has only been shown in 2 cases in this series, both clinically detected. It is possible that further vaginal metastases were present in the non-autopsied cases and even in some cases where the autopsy findings were not very completely recorded. As to distant metastasis in organs other than the lung, they were most frequent in the liver and the brain also splenic metastasis (which is rare in other carcinomas) was shown in 3 out of 11 autopsied cases.

The follow up of this series demonstrates clearly the pronounced difference in prognosis between invasive mole and choriocarcinoma. All 13 patients with invasive mole survived after hysterectomy while only 7 out of 24 choriocarcinoma

patients are symptom-free 6–9 years after the end of the malignancy-producing pregnancy. In the 13 cases which, after the author's revision of the slides, were classed as invasive mole, the original PAD on the hysterectomy specimen was choriocarcinoma in 8 cases—in spite of the fact that the presence of molar villi was mentioned in the histological description in several cases. The results of the follow up stress the importance of separating invasive mole from choriocarcinoma. Although the invasive mole may give rise to regressing lung metastases it rarely if ever causes death if the uterus is removed. Though generally included in the group of chorionic malignancy and referred to as such in this paper the invasive mole is in fact a biologically benign lesion. However it is not possible to exclude, that an invasive mole left in the uterus for an extended period of time may change its character into choriocarcinoma. In such cases the malignant cell proliferation is likely to destroy the remainder of the molar villi. No histologically examined distant metastasis after hydatidiform mole in this series revealed any rests of molar villious structures.

Hertig & Sheldon (1956) stress that the degree of epithelial atypia found in the delivered mole is correlated to the later development of invasiveness or choriocarcinoma. The findings in this material do not confirm this view. It includes 20 cases of delivered mole (cases not primarily treated by hysterectomy) where invasive mole or choriocarcinoma was later diagnosed. When the mole picture in these cases was classed according to Hertig's 3 step grading of atypia, only 5 came into grade 3 (apparently malignant), 3 corresponded to grade 2 (potentially malignant), while 12 belonged to grade 1 (apparently benign). This material also demonstrates a difference in prognosis between the group of choriocarcinoma preceded by mole and the group without proven preceding mole. In the former group 5 out f 10 patients are alive more than 9 years after the mole, while in the latter only 2 out of 14 are living after 6 or 7 years. The group "choriocarcinoma after term or near term delivery" proved especially malignant (9 of 10 patients dead within 18 months). In most f these cases it is probable that the choriocarcinoma developed during the pregnancy and it is possible that the retention of the pregnancy until term or near term is factor promoting the malignant course.

ACKNOWLEDGEMENTS

I wish to express my sincere gratitude to my fellow pathologists who have placed the histopathological material at my disposal and to the Heads of the Gynaecological Centres who have given me access to the clinical records. This investigation has been supported by grant from "Cancerföreningen i Stockholm.

REFERENCES

Acosta-Sison, H. Obst Gynecol *10* 165 1957.
Aries, R. E. & Bertola, F. Obst Gynecol *13* 737 1959.
Brewer J. I. & Gerber A. G. Obst Gynecol *94* 692, 1966.
"Cancer Incidence in Five Continents. U.I.C.C. Report. Springer 1966.
Chan, D. P. C. & Fung, L. S. C. J Obst Gyn Brit C'lth *71* 192, 1964.
Hertig, A. T. & Mansell, H. Hydatidiform Mole and Choriocarcinoma, A F I P's Atlas of Tumor Pathology. Female Sex Organs, Part 1. Washington D.C., 1956.
McRae, D. J. J Obst Gynecol Brit Emp *58* 373 1951.
Novak, E. R. & Woodruff, J. Gyn and Obstetr Pathology 6th edn, Saunders, 1968.
Park, W. W. & Lees, J. C. Arch Path *49* 205 1950.
Public Health in Sweden (Allmän Hälso- och Sjukvård) 1958, Official Statistics of Sweden 1960, Annual Rep. of the National Bord of Health, pp 63–69.
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— 1965 Off. Stat. 1967 pp 97 104.
Ringertz, N. Sjöström, A. Ericsson, J. & Olander, B. Cancer Incidence in Sweden 1958. Stockholm, 1960.
Ringertz, N., Sjöström, A. Tornberg, B. & Swenson, D. Cancer Incidence in Sweden 1959. Stockholm, 1962.
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A MICROANGIOGRAPHIC STUDY OF THE FETAL ARTERIAL VASCULATURE IN THE HUMAN PLACENTA IN UNCOMPLICATED PREGNANCY

Kai Krohn, Björn I. Ivemark and Kalle Salo

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Abstract. The fetal arterial vasculature of 36 normal human placentas was studied by microangiography. There are two fairly readily distinguishable types of intracotyledonary artery. The first intracotyledonary artery (type A) is long and narrow and runs straight from the chorionic space towards the decidua. Its branches run within the same stem in the same or the opposite direction. The second intracotyledonary artery (type B) is thicker and twisted, and its branches extend perpendicularly from the stem. According to the distribution of these two types of arteries, three different groups of cotyledons were distinguished—those with only type A arteries, those with only type B arteries, and those with both types of intracotyledonary arteries. In these mixed cotyledons the type B arteries were always situated in the middle of the cotyledon. A fourth cotyledonary group was also distinguished, which was composed of an irregular mixture of different types of arteries, which could often only be classified with difficulty. Recurrent anchoring arteries could definitely be demonstrated. These were always branches of type B intracotyledonary arteries. In 5 of the 36 placentas spiralling involved almost all the fetal placental arteries.

Conflicting opinions are still held on the pattern of the fetal and the maternal vasculature in the human placenta. These differences probably depend to a large extent on the techniques used. Simple dissection (Bumm, 1890, 1893), injection followed by corrosion (Spanner, 1935), injection with dyes (Boe, 1953) and digestion of the perivascular material with trypsin (Crawford & Fraser 1955) are methods which have been applied to this problem.

Since microangiography can be combined with a histological study of the injected areas, it is a valuable tool for the demonstration of vascular morphology in pathological as well as in normal conditions.

The present article deals with the results of our microangiographic study of the fetal arterial vasculature in the normal placenta. The pathological changes in toxaemia of pregnancy and in maternal diabetes will be described in later publications.

MATERIAL AND METHODS

Thirty-six placentas were obtained from uncomplicated parturitions at the Karolinska Hospital, Stockholm, and the Women's Clinic, University of Helsinki. All the placentas were from full-term, uneventful pregnancies that had resulted in the birth of healthy infants (Table I).

The placentas were injected with a 7.5% aq. suspension of barium sulphate through the umbilical arteries at a constant non-pulsating pressure of about 125 mm Hg. Most (31) of the placentas were injected when fresh, but 5 were frozen and stored at −20°C for various periods before they were thawed and injected (Table II).

The injection was discontinued when no further filling of the placenta was observed. This state was usually reached after 1–3 hours. The placentas were then immersed in 10% neutral formalin for 7 days–1 month.

After fixation the whole placenta was X-rayed (Figs. 1, 2 and 3). The placentas were then sliced at 0.8 cm, and the resulting slices X-rayed (Fig. 4). Since the width of a fetal cotyledon is greater than the thickness of these slices, each cotyledon can usually be seen in several (2–5) successive slices. Areas representing each individual fetal cotyledon were identified, and the number of cotyledons and their vascular patterns recorded (Fig. 4). Samples were then selected from the slices, embedded in Histowax and sectioned at 500–1500 μ. These blocks were exposed with a Machlett OEG X-ray tube at 40 kV and 8 mA on Kodak Maximum Resolution Plates (resolution at least 1500 lines/mm). To obtain a stereo-pair each

Peripheral and central cotyledons. A fetal cotyledon is classified as central when no part of it is in contact with the margin of the placenta, whereas a peripheral cotyledon always reaches the margin of the placenta.

Arteries that first run towards the decidua and after reaching the maternal side of the placenta turn back towards the chorion are called *anchoring arteries.*

Degree of filling. The degree of filling of the placentas with contrast medium was estimated from the macroradiograms of whole placentas and graded as follows:

Group I. Well filled placentas (Fig. 1). About 9/10 or more of the area of the macroradiogram of the whole placenta is filled with contrast medium.

Group II. Moderately filled placentas (Fig. 2). About 1/2 or more of the area of the macroradiogram is filled with contrast medium.

Group III. Poorly filled placentas (Fig. 3). Less than 1/2 of the area of the macroradiogram is filled with the contrast medium.

RESULTS

Degree of placental filling

The number of placentas with different degrees of filling and the relation of filling to the interval between birth and the start of contrast injection



Fig. 4. Macroangiogram of serially sliced, well filled placenta. Two fetal cotyledons in consecutive slices are indicated by arrows.

Table III. *The distribution of peripheral and central cotyledons in well filled, moderately filled and poorly filled placentas*

Degree of filling	Number of placentas	Number of peripheral cotyledons	Number of central cotyledons	Total number of cotyledons
Good	11	106	71	177
Moderate	11	69	68	137
Poor	14	41	28	69

or freezing are given in Table II. Generally the longer the interval between birth and injection the poorer was the degree of filling, but complete filling was sometimes obtained even when this period was more than 1 hour. The frozen placentas were invariably well filled; the period elapsing before the beginning of freezing was less than 1 hour for 3 and less than $^1/_2$ hour for .. placentas (Table II).

Number and distribution of fetal cotyledons

The average number of demonstrable cotyledons was 16.2 ± 5.0 in well filled, 12.4 ± 3.4 in moderately filled and 4.9 ± 3.8 in poorly filled placentas. Table III gives the distribution of peripheral and central cotyledons in the different groups. The ratio between peripheral and central cotyledons was 1.5 in the well filled, 1.0 in the moderately filled and 1.5 in the poorly filled placentas, a sign that the filling of a cotyledon does not depend on the location of the cotyledon in the placenta.

Precotyledonary arteries

The two umbilical arteries (a single umbilical artery was not encountered in any of the placentas) regularly anastomose a few centimetres before the insertion of the umbilical cord into the chorionic plate. Despite this anastomosis, each of the umbilical arteries gives off branches, the allanto-chorionic arteries, to a separate half of the placenta. The branches of the allanto-chorionic arteries, the subchorionic arteries, usually divide into two or three main cotyledonary arteries. Occasionally however a subchorionic artery does not divide but vascularizes only a single cotyledon. The main cotyledonary artery often divides just before entering the cotyledon.

In addition to the main cotyledonary arteries, branches of the subchorionic arteries regularly

Table I *Composition of the series of 36 injected normal human placentas*

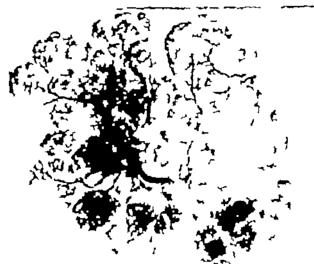
	Mean ± S.E.
Age of mother (years)	26.6 ± 5.2
Duration of pregnancy (weeks)	40.0 ± 1.2
Weight of infant (g)	3 530 ± 418
Length of infant (cm)	50.2 ± 3.5
Weight of placenta (g) prior to injection, including cord and membranes	597 ± 131

Table II *The distribution of placentas into groups according to grade of filling and the correlation between filling and the time elapsing between birth and the start of contrast injection or freezing*

Time elapsing	Well filled placentas	Moderately f lled placentas	Poorly filled placentas
Less than 1/2 hour	3 (2 frozen)	1	0
More than 1/2 hour less than 1 hou	3 (3 frozen)	3	0
More tha 1 hour	5	7	14
Total	11	11	14

block was exposed twice and the blocks were moved from the vertical axis between exposure to give a viewing angle of 9 The stereo-microangiograms were xamined in a stereoscopic viewer Sterant (NIFE), at 7 linear magnification.

After microradiography the sections were re-embedded in paraffin and serially sectioned at 4 μ for microscopic examination.



F g 1 Macroangiogram of well filled placenta.



Fig 2 Macroangiogram of a moderately filled placenta

DEFINITIONS

In eferring to the arteries and the structures of t placenta the following definitions are used.

An *allanto-chorionic artery* is a branch of one of t umbilical arteries and runs in the fetal side of the placen between the chorion and the amnion.

A *subchorionic artery* is a branch of an allanto-chorio ic artery and penetrates the chorionic plate to run in t subchorionic space A subchorionic artery or its bran which vascularize a sing fetal cotyledo is called main cotyledonary artery

A *fetal cotyledon* is a unit f fetal essels compos of arious types of arteries in the normal placenta ar always extends from the subchorionic space t the decidu basa is



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In addition to the main cotyledonary arteries branches of the subchorionic arteries regularl



Fig. 5. Microangiogram showing type A intracotyledonary arteries. × 1_.

form small fetal units, less than 5 mm in diam ter which contain villi but are less regular in form than the ordinary fetal cotyledon.

Vascular pattern of cotyledon

Great irregularity was observed in the vascular pattern of the fetal cotyledons in all the placentas studied. However the intracotyledonary arteries could usually be divided into two types. The types could b_ distinguished from the macroangiograms but the differences were clearer in the microangiograms.

Type A fetal intracotyledonary arteries (Figs. 5 and 6). These are long, narrow arteries which usually run parallel to one another from the chorionic side of the placenta towards the decidual side. The calibres of the arteries range from 100 to _50 . The arteries give rise to only a few branches. The branches are always of small calibre and always run within the same stem and usually in the same direction as the main artery. Occasionally the branches turn to run in the opposite direction to the main artery but still in the sa stem.

Type B fetal intracotyledonary arteries (Figs. and 9). These arteries are wider and range fro 250 to 500 *μ* in diameter. They usually gi rise to several branches of different size. The branches leave the stem at right angles to t main artery occasionally at an acute angle, a turn in the opposite direction to th_ main arter Very often the branches run a few millimetr within the same stem as the main artery befo they separate (predivision of arteries inside t stems, Bøe 1952).

On the basis of their arterial pattern the coty dons can be classified into four groups.

Group 1. This is composed of stems containi only type A intracotyledonary arteries (Figs. 6 and 7).

Group 2. This is composed of stems containi only type B intracotyledonary arteries (Figs. and 9).

Group 3. This is composed of both types o



Fig. 6. Histological secti depicting tw m th type A intracotyledonary arteries (arrows) and adjoining ar terioles (triangles) ithin the same stem 0 Lillie allochrome connecti tissue stain



Fig 7 Microangiogram showing group 1 fetal cotyledon. 6.

intracotyledonary arteries. Type A arteries always run in the periphery and type B arteries in the central part f the cotyledon the latter are gener ally fewer in number I some cotyledons only one type B intracotyledonary artery was observed in the centre (Fig 10 a and b).



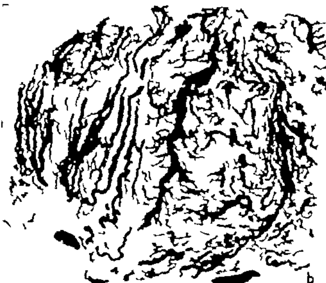
Fig 8 Microangiogram of group 2 fetal cotyledon ... type B intracotyledonary artery Predivision of arteries ... stem is indicated by the arrows. 3



Fig 9 Histological section demonstrating predivision of arteries within stem. Two branches (B) leave the stem and the left one turns upwards. The arrow indicates small arterioles ... the stem. 15 Lillie allochrome connective tissue stain.



Fig. 10 a and *b*. Microangiogram of a group 3 fetal cotyledon with type A intracotyledonary arteries in the periphery and type B intracotyledonary arteries in the middle of the cotyledon. × 3



Group 4. In this group the vascular pattern is mixed.

Because of poor filling, some of the cotyledons could not be classified at all. Table IV lists the distribution of the cotyledons with different vascular patterns in well filled, moderately filled and poorly filled placentas. The results show a clear correlation between the filling of the placenta and the number of cotyledons with type A intracotyledonary arteries. In poorly filled placentas no fetal cotyledons of group 1 were observed and the number of cotyledons of group 3 was 6 compared with 35 % in the completely filled placentas. The explanation for this must be that the *narrow type A intracotyledonary arteries are more* difficult to fill than the wider type B intracotyledonary arteries.

Table IV. *Distribution of cotyledons with different arterial types in different parts of the placentas in relation to the degree of filling with contrast medium*

	Well filled placenta				Moderately filled placenta				Poorly filled placentas			
	Centre		Periphery		Centre		Periphery		Centre		Periphery	
	N		N		N		N		No.		No.	
Group 1	13	18.3	15	14.2	3	4.4	0	0	0	0	0	0
Group 2	10	14.1	22	20.8	15	22.1	11	16.0	5	17.9	9	22.0
Group 3	31	43.7	10	[illegible]	20	29.4	1	[illegible]	1	1.6	3	7.3
Group 4	16	[illegible]	38	35.8	4	35.3	31	30.4	9	32.1	11	26.8
Poorly filled cotyledons	1	1.4	1	0.9	6	8.8	16	23.2	13	46.4	18	43.9
Total	71	100.0	106	100.0	68	100.0	69	100.0	28	100.0	41	100.0
	177				137				69			

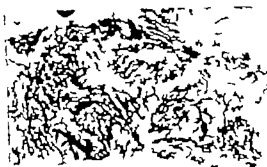


Fig. 11. Macroangiogram of group 4 fetal cotyledon with irregularity of the intracotyledonary arteries. 3



Fig. 13. Macroangiogram showing several anchoring arteries. The symbols in Figs. 13 and 14 correspond to each other. 5

Anchoring arteries

Anchoring arteries were observed only in stems that fixed the placenta to the decidual plate (Figs. 12, 13 and 14). They always originated from type B intracotyledonary arteries. The proportion of cotyledons containing such arteries, calculated from the macroangiograms, was 31 among the total of 383 cotyledons (8%). Table V gives th distribution of anchoring arteries in the different groups of cotyledon and in placentas with different degrees of filling.

Spiralling of the fetal arteries of th placenta

Numerous spiral arteries were seen in 5 placentas (Fig. 15). This spiralling was observed in every cotyledon well as in the subchorionic arteries. The allantochorionic arteries were not spiralled.

In the cotyledons of the 5 placentas practically all the intracotyledonary arteries were spiralled.



Fig. 1 Macroangiogram of cotyledon with several anchoring arteries. 3

The calibre of the spiralled arteries was greater than that of the unspiralled ones. The number of arteries in a cotyledon was reduced in the placentas with arterial spiralling. Four of the placentas with arterial spiralling were in the group of well filled placentas and these had been frozen before injection. One of the placentas was poorly filled, it had not been frozen before injection, but injected in the usual way more than 1 hour after the birth of the infant.

In addition to this spiralling which involved the cotyledons, spiralling limited to a few subchorionic arteries was seen in 14 placentas. In these placentas the intracotyledonary arteries were normal.

DISCUSSION

In the present study the fetal cotyledon was defined as a separate unit, which in angiograms appears to have a relatively uniform size and shape. A main cotyledonary artery was defined as a subchorionic artery or its branch vascularizing a cotyledon. This means that the number and size



Fig. 10 a and *b*. Microangiogram of a group 3 fetal cotyledon with type A intracotyledonary arteries in the periphery and type B intracotyledonary arteries in the middle of the cotyledon. ×3



Group 4. In this group the vascular pattern is mixed.

Because of poor filling, some of the cotyledons could not be classified at all. Table IV lists the distribution of the cotyledons with different vascular patterns in well filled, moderately filled and poorly filled placentas. The results show a clear correlation between the filling of the placenta and the number of cotyledons with type A intracotyledonary arteries. In poorly filled placentas no fetal cotyledons of group 1 were observed and the number of cotyledons of group 3 was 6 % compared with 35 % in the completely filled placentas. The explanation for this must be that the narrow type A intracotyledonary arteries are more difficult to fill than the wider type B intracotyledonary arteries.

Table IV. *Distribution of cotyledons with different arterial types in different parts of the placentas in relation to the degree of filling with contrast medium*

	Well filled placentas				Moderately filled placentas				Poorly filled placentas			
	Centre		Periphery		Centre		Periphery		Centre		Periphery	
	N		N		N		No		N		N	
Group 1	13	18.3	15	14.2	3	4.4	0	0	0	0	0	0
Group [illegible]	10	14.1	[illegible]	[illegible]	15	22.1	11	16.0	5	17.9	9	22.0
Group 3	31	43.7	30	[illegible]	[illegible]	[illegible]	[illegible]	10.4	[illegible]	[illegible]	3	7.3
Group 4	16	22.5	38	35.8	4	35.3	31	30.4	9	[illegible]	11	[illegible]
Poorly filled cotyledons	1	1.4	1	0.9	6	8.8	16	23	13	46.4	18	43.9
Total	71	100.0	106	100.0	68	100.0	69	100.0	28	100.0	41	100.0
	177				137				69			

sumed that techniques which depend on injecting the vessels with hardening materials will fail to demonstrate these vessels. This may explain why Spanner using the corrosion cast method, succeeded in demonstrating only the "chandelier" arteries.

The formation of the gross structure of the fetal cotyledon with its hollow centre (intracotyledonary space), demonstrated by several investigators (Wilkin, 1954 Ramsey 1962 Freese, 1966 Reynolds, 1967), has been considered to be determined by the direction of the maternal blood flow in the intervillous space (Freese, 1966 Reynolds, 1967). It is suggested that the high systolic arterial pressure injects the maternal blood through this intracotyledonary space, towards the chorionic plate, from which the blood slowly descends towards the decidua through the peripheral parts of the cotyledon.

It is tempting to speculate that the direction of the maternal blood flow influences the genesis of the different types of intracotyledonary artery. Thus, stems containing the type B intracotyledonary arteries would be formed where a high systolic pressure injects maternal blood rapidly towards the chorion, e.g. in the opposite direction to the fetal blood flow and it is easy to understand why under such conditions, branches of the main stem would run perpendicularly or even turn in the opposite direction. Stems containing type A intracotyledonary arteries, on the other hand, would probably be formed where the maternal blood runs slowly towards the decidua and thus in direction parallel to the fetal blood flow. According to this hypothesis, the main direction of the maternal blood flow differs in the different types of cotyledons. In the cotyledons containing both types of intracotyledonary arteries type A always run in the periphery and type B in the centre of the cotyledon. To apply our hypothesis, then, the direction of the maternal blood flow would be towards the chorion in the centre and towards the decidua in the periphery of the cotyledon. Where only one type of intracotyledonary artery is present, the maternal blood would flow only in one direction within one cotyledon. In the cotyledons where no regular arrangement of intracotyledonary arteries is present, the direction of the maternal blood flow probably varies.

It is also possible that the irregularity of the small villous structures of the subchorionic space is due to the slow rate of the maternal blood flow in this part of the placenta.

Crawford (1956) stated that arteries in the fixing stems do not fill with contrast after they have reached the decidual plate. Our work, however clearly demonstrates that the fixing stems as well as their anchoring arteries frequently turn up towards the chorion and even give off branches after touching the decidua. Thus these vessels exhibit the chandelier arrangement described by Spanner (1935). However recurrent anchoring arteries of this type could be seen in only some of the cotyledons. This may partly depend on the fact that the macroangiograms used for estimating the number of cotyledons with anchoring arteries were not clear enough for detailed studies.

Anchoring arteries were formed exclusively from the type B intracotyledonary arteries. The fact that no such arteries were seen in the type A intracotyledonary arteries may be due to the difficulty of filling these arteries.

Spiralling of the entire arterial vasculature of the placenta was seen in 5 placentas. This type of spiralling seems to be independent of spiralling of the subchorionic arteries, which has previously been described by Romney & Reid (1951). According to him, this spiralling may be due to the trophic stimulus of steroid hormones. The cause of the spiralling of the entire fetal arterial vasculature in the placenta is unknown. It can be questioned whether freezing had any influence on the degree of spiralling and the width of the arterial lumen. Four of the well filled placentas had extensive spiralling and the lumina of their intracotyledonary arteries were wide all of these four placentas had been frozen.

ACKNOWLEDGEMENTS

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REFERENCES

Bøe, F. Studies on the vascularization of the human placenta. Acta Obstet Gynec Scand 32, Suppl. 5. 1953.

Bumm, E. Zur Kenntniss der Uteroplacentaren Gefässe. Arch Gynäk 37 1 1890.



Fig 14 Histological section of the same area as in Fig. 13 showing the left anchoring artery turning up after fixing the stem to the decidua (*arrow* the turning point; dark sta branch turning upwards; D decidua) 15 Hematoxylin-eosin.



Fig 15 Spiralling f subchorionic and intracotyledonary arteries. Allanto-chorionic arteries are not spiralled. 3.

of the cotyledons were relatively uniform in dif ferent placentas, despite the varying origin of the main cotyledonary artery i.e. either as a direct branch of an allanto-chorionic artery or as a branch of a subchorionic artery

Classified according to their arterial pattern, there are four different groups of fetal cotyledons, three of which can readily be distinguished ac cording to whether they are composed of the one or the other of the two types of intracotyledonary arteries or of a combination of the two The type A intracotyledonary artery running straight from the chorionic part of the cotyledon towards the decidua, resembles the branches of a weeping willow tree. The type B intracotyledonary artery with branches running perpendicularly and oc casionally turning in the opposite direction to the main artery can b considered an example of the chandelier type of vessel described by Spanner (1935)

The distribution of the different groups of co- tyledons in placentas with different degrees of filling may explain the contradictory results in previous reports concerning the structure of ves- sels forming the fetal cotyledon. The number of cotyledons with type A arteries was fewer in placentas which were poorly filled. It can be as

Table V *Cotyledons containing anchoring stems according to their macroangiographical appearance*

Filling	Group 1	Group 2	Group 3	Group 4	Poorly filled cotyledons	Total	
Good							
Centre	0	0	5	3	1	9	15
Periphery	0	1	3	3	0	6	
Moderate							
Centre	0	1	1	3	0	5	13
Periphery	0	3	3	1	1	8	
Poor							
Centre	0	0	0	0	0	0	3
Periphery	0	1	1	1	0	3	

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PREOPERATIVE ANTICOAGULANT TREATMENT IN GYNAECOLOGICAL SURGERY

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Abstract. The feasibility of preoperative anticoagulant treatment in connection with gynaecological surgery was studied in a series of 59 patients who were considered to have a predisposition to thromboembolic complications. The anticoagulant drug used was warfarin sodium (Marevan®) and Owren Thrombotest (TT) method was employed in the control of the treatment. Clinically detectable venous thrombosis or pulmonary embolism did not occur in the series. In 1 case a non-fatal myocardial infarction was diagnosed postoperatively. There were no deaths in the series. Clinically significant haemorrhagic complications occurred in 5 cases, but could be controlled in all instances. Our experience indicates that preoperative anticoagulant treatment is feasible in connection with gynaecological surgery. If the anticoagulant treatment is supervised carefully it does not cause any undue increase in the risk of bleeding complications. However, careful haemostasis during surgery is imperative in patients receiving preoperative anticoagulant treatment. A TT level of 10–20% seems to be suitable in preoperative anticoagulant treatment.

In spite of prophylactic measures, thromboembolism remains a significant postoperative complication. Indeed, in some circumstances the incidence may be even higher than formerly, since advances in anaesthesiology and pre- and postoperative care now enable surgical procedures to be undertaken on older patients and those with cardiovascular or other diseases which predispose thromboembolism. Numerous reports show that the incidence of thromboembolic complications can be reduced by postoperative oral anticoagulant treatment. However, series have also been published, in which no effect of postoperative anticoagulant treatment on the incidence of pulmonary embolism could be demonstrated (Anlin et al. 1968). This is obviously due to the fact that in a considerable number of cases pulmonary embolism develops as early as within the first 2 days following operation (Coon et al., 1959; Keller 1967). It seems possible that the primary venous thrombosis often develops during the time of anaesthesia and operation.

A large body of data is available on the use of oral anticoagulant treatment in connection with mitral valvotomy (e.g. Müllertz et al., 1954; Storm et al., 1955; Smith et al., 1965). Today it is the rule that in cases where the risk of thromboembolism is particularly great, as in patients with atrial fibrillation or in those with a history of thromboembolic episodes, oral anticoagulant treatment is given for several weeks preoperatively and the operation is performed under continuous anticoagulant treatment. The use of anticoagulant prophylaxis has almost completely abolished arterial embolism originating in the left atrium as well as venous thrombosis and pulmonary embolism, without increasing the operative risk.

Preoperative anticoagulant treatment has also been adopted in other kinds of surgery. Considering, however, the increasing use of surgery in cases where the risk of thromboembolic complications is obvious, it is surprising that this mode of anticoagulant treatment has not been more widely introduced. Müllertz et al. (1954) and Storm et al. (1958) successfully used preoperative oral anticoagulants in thoracic surgery. Storm et al. (1957) and Wieberdink (1967) used a similar regime in connection with vascular operations. Favourable results with preoperative anticoagulant treatment in connection with abdominal operations have been published by Storm (1961), Kluft et al. (1965) and Rosiad et al. (1963).

Gynaecological operations are known to be associated with a particularly high risk of thrombo-

— Über die Entwicklung des mütterlichen Blutkreislaufes in der menschlichen Plazenta. Arch Gynäk 4 11 181 1893
Crawford, J M. & Fraser A. The foetal placental circulation. A technique for its demonstration. J Obst Gynaec Brit Emp 62, 896, 1955
Crawford, J M. The foetal placental circulation. Part II. The gross anatomy J Obst Gynaec Brit Emp 63 87 1956.
— The foetal placental circulation. Part III. The anatomy of the cotyledons. J Obst Gynaec Brit Emp 63 542, 1956.
Freese U E. The fetal-maternal circulation of the placenta. Am J Obst Gynec 94 354 1966.
Freese U E, Ranniger K. & Kaplan, H. The fetal maternal circulation of the placenta. Am J Obst Gynec 94 361 1966.
Ramsay E. M Circulation in the intervillous space of the primate placenta. Am J Obst Gynec 84 1649 196_
Reynolds, S. R. M. Derivation of the vascular elements in the fetal cotyledon of the hemochorial placenta. a contribution to the theory of placental morphogenesis. Anat Rec 157 43 1967
— Formation of fetal cotyledons in the hemochorial placenta. Am J Obst Gynec 94 425 1966.
Romney S. L. & Reid, D E. Observations on the fetal aspects of placental circulation. Am J Obst Gynec 61 83 1951
Spanner R. Mütterlicher und kinderlicher Kreislauf der menschlichen Plazenta und seine Strombahnen. Z Anat Entwickl-Gesch 105 163 1935
Wilkin, P Contribution à l'étude de la circulation placentaire d'origine foetale. Gynéc et obstét 53 _39 1954

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a clinically insignificant haematoma was observed postoperatively in the wound area. Significant bleeding occurred postoperatively in 5 cases, 3 of which required surgical procedures. These will be reported below because they elucidate the problems associated with preoperative anticoagulant treatment.

Case 1. A 55-year-old patient with urinary incontinence. Owing to large varicose veins, pre-operative anticoagulant therapy was instituted. Marshall-Marchetti operation was performed. On the next day a haematoma, the size of a fist, was observed in the wound area. In the morning of the same day the TT value was 8%. The wound was reopened and the haematoma was evacuated. The subsequent course was uneventful. Vitamin K was not given and the TT remained within the therapeutic range throughout.

Case 2. A 67-year-old patient with total prolapse of the uterus. Anticoagulant therapy was started preoperatively because of cardiac insufficiency. Total vaginal hysterectomy and vaginoplasty were carried out. Two days later the patient exhibited obvious signs of shock. On rectal examination a mass, the size of a fist, was observed attached to the vaginal stump. In the morning of the same day the TT was 8%. Laparotomy revealed a haematoma, arising from a small atrophic piece of uterus, which had not been removed at the first operation. This was excised and both adnexa were removed. The blood loss was estimated at about 700 ml. It was corrected by blood transfusions, and in addition the patient was given 20 mg of vitamin K_1 intravenously. As a result of the administration of vitamin K and blood transfusions and the cautious warfarin therapy the TT rose above the therapeutic level for 4 days. Anaemia developing post-operatively was corrected by blood transfusions, and the patient was discharged 28 days after operation.

Case 3. A 71-year-old patient with metrorrhagia. A specimen from the uterine cavity obtained by curettage showed reticular sarcoma. Since the patient was old and had cardiac insufficiency anticoagulant treatment was started prior to operation. Total abdominal hysterosalpingectomy was carried out. On the morning of operation the TT was 8%. Immediately after operation profuse bleeding from the vaginal stump commenced. The vagina was tamponed in the operating theatre, and the patient was given 20 mg of vitamin K_1 intravenously. In addition she received three units of blood. The haemorrhage ceased and the tampon was removed the next day. On the third and fourth days after the operation the TT exceeded 25%.

In another 2 cases a haematoma was observed clinically in the operative field after total hysterectomy but no surgical procedures were required. In these cases the TT remained throughout above 10%.

The deviation of the post-operative haemoglobin values from the pre-operative values appears in Table V. Ten patients received blood transfusions during or after operation.

Thromboembolic complications. In no case did

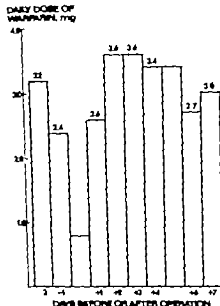


Fig. 2. The mean daily dose of warfarin before and after operation

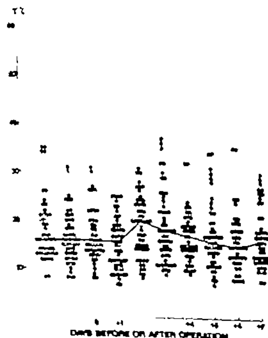


Fig. 1. TT values and their median before and after operation

Table I *Age distribution of patients given preoperative anticoagulant therapy*

Years	No of patients
40–49	6
50–59	10
60–69	26
70–79	16
80 <	1
Total	59

Table II *Gynaecological diseases of operatively treated patients given preoperative anticoagulant therapy*

Prolapse of the uterus	33
Benign neoplasm of the ovary	10
Malignant neoplasm of the uterus	5
Benign neoplasm of the uterus	4
Stress incontinence of urine	2
Malignant neoplasm of the ovary	1
Adenomyosis	1
Endometriosis of the ovary	1
Incisional hernia	1
Bilateral pyosalpinx	1
Sigmo-ovarian fistula	1
Legal abortion and sterilization	1

embolic complications, especially in elderly pa tients. So far hardly any data have been published on the use of preoperative anticoagulant treatment in gynaecological surgery In this paper an attempt is made to elucidate the practicability of preoperative anticoagulant treatment in connec tion with gynaecological operations performed on patients who are elderly or have a predisposition to thrombosis.

MATERIAL AND METHODS

A total of 1 186 gynaecological patients w th mean ge of 41.. years were operated on at the Central Hospital of Middle Finland during the period Nov 11 1965 – Dec. 31 1967 Preoperative anticoagulant therapy was given to 59 patients who were considered to have predisposi tion to thromboembolism as result f cardiac insuffi ciency obesity previous history of thromboembolism, large varicose veins or ge The ge range f these patients was from 42 t 8? years, the mean being 65.0 years. Tables I, II, III and IV show the ge *distribution*, classification according to gynaecological diagnosis, *other* concurrent diseases nd operations performed in this group

The anticoagulant used was warf rin sodium (Marevan®). The level of the prothrombin comple clotting factors as determined daily t 8 9 m. by Owren Thrombotest (TT) method. The daily dose of anticoagulant was given at 6 p.m. The treatment was begun with a single dose of 12–14 mg and continued after one day's interval with a daily maintenance dose. It was attempted to maintain a TT level of 10–25%.

RESULTS

Maintenance of the therapeutic level. The TT values are shown in Fig. 1 The mean daily doses of warfarin appear in Fig. 2. The treatment was not completely successful inasmuch as immediately after operation the TT values tended to rise above the therapeutic level in some cases. In 27 cases the TT value remained under 25% throughout the post-operative period. In 23 cases the TT value exceeded the upper limit of the therapeutic range once or twice If values outside the therapeutic range were noted three times or more the treatment was regarded as unsuccessful. This oc curred in 9 cases. Sixteen patients had TT values under 10% during treatment.

Bleeding In general the blood loss at opera tion was not greater than usual In 5 cases diffuse bleeding caused the operator some trouble but clinically it was of no significance In 9 cases

Table III *Concurrent diseases in patients given preoperative anticoagulant therapy*

Congestive heart failure	[illegible]
Varicose veins	15
Obesity	7
Arterial hypertension	6
Superficial thrombophlebitis	2
Bronchial asthma	2
Hemiplegia	1
Thyrotoxicosis	1

Table IV *Operations performed on patients given preoperative anticoagulant therapy*

Pelvic floo repair	18
Total vaginal hysterectomy	13
Total bdominal hysterectomy	12
S btotal bdominal hysterectomy	6
Total bdominal hysterectomy Pelvic floor repair	2
Repair of femoral hernia	
Total bdominal hysterectomy	
Marshall–Marchetti operation	1
M rshall M rchetti operation	1
Unilateral salpingo-oophorectomy	1
V hectomy	1
Abdominal hysterectomy nd sterilization	1
E ploratory laparotomy	1
Total	59

these cases the TT was under 10%. At least in 1 case the cause of the bleeding was surgical. Since in gynaecological operations the wound surface is often extensive, there is always a risk of diffuse bleeding. For this reason it seems obvious that when preoperative anticoagulant therapy is used in connection with gynaecological operations, a TT level of 10–20% should be maintained. If during treatment the TT values drop slightly below the therapeutic range, immediate administration of vitamin K is not indicated. If no signs of a haemorrhagic tendency are observed, it is often sufficient to check the TT values frequently and withhold the anticoagulant. If the TT values show a markedly declining trend, the situation may be improved by administering small doses (1–2 mg) of vitamin K. If bleeding results from over dosage, 10–20 mg of vitamin K should be given intravenously.

The present series is not large, but it was intentionally selected so as to include only patients considered to have a predisposition to thromboembolism. From the standpoint of thromboembolism prophylaxis the treatment was successful, considering that in no case did clinically observable venous thrombosis or pulmonary embolism develope. One patient developed myocardial infarction post-operatively. However it is a well-known fact that this complication is not always prevented by anticoagulant therapy. Although an untreated control group was not included in our study, the present results seem to corroborate the favourable reports which have been published on the use of preoperative anticoagulant treatment in connection with other kinds of surgery. It may therefore be assumed that in gynaecological surgery the incidence of thromboembolism can be reduced to a minimum if the operation is performed under anticoagulant treatment in those cases where the thromboembolic hazard is considered to be great. It is not possible and probably not even indicated, to extend preoperative anticoagulant prophylaxis to all surgical patients. The essential problem in assessing the indications for preoperative anticoagulant treatment lies in the preoperative clinical assessment of the risk of thromboembolism. In general, cardiac insufficiency, previous thromboembolic episodes, varicose veins and obesity are considered as factors increasing the hazard. In addition, Timonen et al. (1966) emphasized the significance of advanced age, the basic disease and the type of surgical procedure. These authors stated that carcinoma, and in particular major operations performed by the abdominal route, increase the risk. Preoperative anticoagulant therapy should be regarded as contraindicated in the presence of the same factors which in general constitute contraindications to anticoagulation: haemorrhagic diathesis, severe disease of the liver parenchyma, a fresh ulcer of the stomach or duodenum and severe hypertension.

REFERENCES

Antlitz, A. M., Valle, N. G. & Kosai, M. F. The effect of prophylactic anticoagulant therapy on the incidence of postoperative pulmonary infarction. Southern Med J *61* 307 1968.

Coon, W. W. & Coller, F. A. Epidemiological considerations in thromboembolism. Surg Gynec Obst *109* 487 1959.

Keller, J. Bergmann: Ist die perioperative Antikoagulantien-Prophylaxe wirklich optimal? Zbl Gynäk *89* 67 1967.

Kluft, O., Storm..., W., deVries, S. I. & Wiebenga, J. The post-operative dip in per-operative anticoagulation. Thrombos Diathes Haemorrh *13* 218. 1965.

Mullertz, S. & Storm, O. Anticoagulant therapy with Dicoumarol maintained during major surgery. Circulation *10* 213, 1954.

Rosstad, H. & Myhre, E. Surgery during anticoagulant treatment. Acta Med Scand *173* 115 1963.

Saarela, M., Juvela, J., Pyörälä, K. & Mustala, O. Absorption of warfarin by normal and atrophic gastric mucosa. Scand J Clin Lab Invest *23* Suppl 108 43 1969.

Szekely, B., Umapathy, A., Bentall, H. H. & Cleland, W. P. Anticoagulants and mitral valvotomy. Brit Heart J *27* 618 1965.

Stephenson, S. F. Anticoagulants and mitral valvotomy: 5-year survey. Thorax *21* 38, 1966.

Storm, O. Anticoagulant protection in surgery. Thrombos Diathes Haemorrh *2* 484, 1958.

Storm, O., Aagaard, P., Lindenberg, J. & Dons, N. Administration of dicoumarol and marcoumar during operation to prevent postoperative thromboembolic complications in patients over 50 years of age. Acta Chir Scand. Suppl. 283 107 1961.

Storm, O. & Gammelgaard, P. A. Antithrombotic treatment in vascular surgery. Acta Chir Scand *113* 460 1957.

Storm, O. & Hansen, A. T. Mitral commissurotomy performed during anticoagulant prophylaxis with dicoumarol. Circulation *12* 981 1955.

Table V *Post-operative decrease of haemoglobin (g/100 ml) in patients given continuous anticoagulant therapy*

	No. of patients
No decrease	17
Decrease < 0–9	12
Decrease 1–1 9	13
Decrease 2 –.9	8
Decrease ≥ 3 0	9
Total	59

venous thrombosis or clinically demonstrable pul monary embolism develop post-operatively A 60-year-old patient, who had been under treatment for cardiac insufficiency and thyrotoxicosis before operation, developed post-operative myocardial infarction from which she recovered. No patient in this series died.

DISCUSSION

The success of anticoagulation is greatly dependent on the experience of the doctor in charge of the treatment. As regards the present series, five dif ferent doctors without any previous experience of preoperative anticoagulant treatment parti cipated in the supervision. Therefore our results apparently give a fair idea of the possibilities of using preoperative anticoagulant treatment in an ordinary hospital Initially the post-operative dos age tended to be too low and TT values rose in some cases above the therapeutic level With in creasing experience values within the therapeutic range were more successfully maintained. It is obvious that still better results would have been obtained if the treatment had always been supervised by the same doctor

The full prophylactic effect of oral anticoag ulant therapy is not attained until 5 to 7 days after its institution, although usually TT values within the therapeutic range are noted within 2 days. During the initial stage of the treatment it is mainly a rapid drop in factor VII level that is registered by the methods of determination used, since the half-life of this clotting factor is shorter than that of the other clotting factors which de pend on vitamin K. Factor IX is the next to drop to the therapeutic level Factor X and prothrombin are slower in this respect Consequently anti-coagulant therapy intended to be continued durı surgery should preferably be started a week befo operation. In this way the patient's individu anticoagulant requirement may be adequately a sessed pre-operatively In some of the pres cases the preoperative anticoagulant treatment h to be curtailed owing to the shortage of beds the gynaecological ward. However the thera was never started later than 4 days before ope tion.

An operation tends to reduce the anticoagul requirement (Storm et al 1957 Kluft et a 1965 Wieberdink, 1967) From the standpoint dosage this implies a problem, if the patien individual anticoagulant requirement under norm conditions is not known before operation. In t series the average maintenance dose of warfa was relatively low about 3 mg. This seems to attributable to the fact that the majority of t patients were over 60 years of age and that patients out of 59 showed cardiac insufficien The safety of preoperative anticoagulant treatme may be enhanced by checking the TT value least twice a day post-operatively if it shows a tendency to deviate from the therapeutic ran If it proves necessary at operation to adminis large volumes of blood, the TT level tends to r (Thies, 1961 Stephenssen, 1966 Wieberdi 1967) It is also noteworthy that certain sim taneously administered drugs, e.g. salicylat phenylbutazone and certain steroids and antib tics, may reduce the anticoagulant requireme After a gynaecological operation the antico ulant may be given by mouth unless the pati vomits. Gastrointestinal absorption of warfa sodium is rapid and complete. This drug is a sorbed even from the stomach (Siurala et a 1969). If vomiting occurs after operation, warfa may be given intravenously The dosage is t same as for oral administration

In the present series 10–25% were chosen the therapeutic TT level This implies perha too cautious a line of anticoagulant therapy T upper limit of the therapeutic range original recommended by Owren, i e 25% may be t high for adequate prophylaxis. Wieberdink (196 adopted a lower therapeutic level i.e 8–1. a he stated that only a drop of the TT to under 5 results in a real risk of haemorrhage In the pre ent series significant bleeding occurred in 5 case 3 of which required surgical procedures. In a

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BILATERAL MULTIPLE LUTEIN CYSTS IN NORMAL SINGLE PREGNANCY

Report of a Case

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Abstract. A case of normal single pregnancy combined with bilateral multiple lutein cysts in the ovaries is reported. Similar cases in the literature are reviewed.

The majority of reports to date on bilateral multiple lutein cysts in the ovaries refer to their common association with abnormal pregnancy. Thus this condition is found in about 50% of women with hydatidiform mole and choriocarcinoma (Baird, 1950). It has been seen together with erythroblastosis of the fetus (Lerner et al., 1958, Rabinowitz et al., 1961), in multiple pregnancies (Weigle & Thatcher 1955, Watson & Demick, 1959) and in pituitary dysfunction (Vago et al., 1964).

Recently there have been a few reports of bilateral multiple lutein cysts associated with normal single pregnancies (Table I). The earlier experience of this condition has led to diagnostic and therapeutic problems in these "normal" cases, which might justify a new case report together with some notes from the literature.

AUTHOR'S CASE

A 26-year-old primigravida with regular menstrual cycles. No hormonal treatment. LMP early December 1963. At antenatal care clinic March 3, 1964 the size of the uterus equalled an early 4 months' pregnancy. T the right was palpated cystic mass about 15 by 15 cm and to the left a similar mass about 8 by 8 cm. HCG 300 000 IU/l. Oestrogen 7.5 mg/24 hours. Exploratory laparotomy was performed on March 5. Both ovaries were found to be transformed into numerous thin-walled cysts, the size ranging from about 1 cm in diameter to about 4 cm in diameter and containing slightly yellow translucent fluid and some with slightly haemorrhagic fluid. The size of the masses and the uterus were as estimated above (see Fig. 1).

It was decided to treat the ovaries conservatively. The contents of the cysts were aspirated by needle and syringe. A biopsy was taken from the right ovary. Microscopic examination showed: Cysts of follicular origin with varying degree of luteinization (Fig. 2).

After the operation the patient was followed carefully and the pregnancy progressed normally. Some hormonal analyses were undertaken and the values are given in Table II.

A living girl, 2830 g, was delivered normally on September 13, 1964. The placenta was grossly normal. Eight weeks after delivery examination revealed uterus of normal size. The ovaries were also normal.

COMMENTS

Only a few cases of normal single pregnancies accompanied by bilateral multiple lutein cysts are reported. As shown by the previous reports, there will often be difficulties in deciding what to do in



Fig. 1. Macroscopic picture. Uterus and polycystic ovaries, 4th month of pregnancy.

Thies, H A. Postoperative Blutgerinnungsstörungen im Zusammenhang mit Transfusionen und Infusionen. Zbl Chir *86* 1211 1961
Timonen, S., Hillesman, V & Nieminen, U Postoperative profylaxis of thromboembolism with warfarin. Ann Chir Gynaec Fenn *55* 81 1966.
Wieberdink, J Safe pre-operative anticoagulation. Thorax *22* 567 1967

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Fig. Microscopic picture. Cysts of follicular origin with varying degree of luteinization.

Table I. *Bilateral multiple lutein cysts in cases of normal single pregnancy literature review*

Author	Age and parity	Short case histories
Jones & Huston, 1961	21 year-old I grav	Abdominal pains and pelvic mass found in 12th week of pregnancy Exploratory laparotomy performed. Spontaneous abortion eeks poster
Rudolph & Barnett, 1956	30-year-old I grav	Lower abdominal pain in 12th week of pregnancy Mass palpated. Laparotomy 150 cc of bloody fluid in the pelvis. Right ovary with numerous small cysts and 10 cm in diam., twisted. Left ovary 8 cm in diam. of the same appearance. Right oophorectomy and 3 4 of the left ovary was resected. Delivery t term, girl 10 lb. 4 oz. Placenta grossly normal.
Shettles, 1963	22-year-old I gra	Multiple lutein cysts in both ovaries found at Caesarean section. Ovaries left intact. Delivery—normal single baby 6 weeks post partum no evidence of ovarian enlargement but at a second pregnancy terminated by Caesarean section, the thecalutein cysts of the ovaries had recurred.
Bergman, 1963	21 year-old I gra	Pelvic pains in 10th week of pregnancy Mass palpated. Laparotomy showed that both ovaries had developed f to fist-sized multicystic masses. The entire cystic left o ary was removed and the right ovary was resected. Normal delivery—girl 2 550 g.
Pa ker & Fisher 1961	1 31-year-old I gra	Pelvic masses found at term. Caesarean section. Bilateral enlarged ovaries with multiple cysts—21 12.5 cm and 14 11 6 cm. Frozen section from one ovary was reported as granulosa cell tumour and total bdominal hysterectomy and bilateral salpingo-oophorectomy was performed. Subsequent histopathology review revealed multilocular lutein cysts. Normal baby—girl 3 370 g.
Parker & Fisher 1961	2. 27 year-old III grav	At Caesarean section at term (repeated for 3rd time for contracted pelvis) a cystic left ovarian tumour 10 cm in diameter was found. The right ovary contained multiple small cysts and measured 3 by 5 cm. Left oophorectomy and right ovaria biopsy were performed. Permanent microscopic sections from the ovaries were believed to represent a granulosa cell tumour Because of potential malignancy the patient was advised to undergo an abdominal hysterectomy and right salphingo-oophorectomy This was done months later Later review of the slides revealed theca cells *with a normal granulosa component.* Normal baby—girl 3 000 g.
Girouard, 1964	23-year-old I gra	Admitted at term in labour The fetal head failed t negotiate the pelvic inlet. Caesarean section. Bilateral m ticystic ovaries. 10 12 and 8 10 cm. *Each of the ovaries was bisected and studied microscopically*—showed multiple theca lutein cysts with luteinization of the theca cell layer principally also the granulosa cell layer was involved in some areas Placenta, ormal grossly Microscopic examination revealed less evidence of maturation than is ordinary Baby normal—girl 5 lb 1.5 oz.
Kesler & Callagan, 1967	16-year-old I gra	Admitted t 10 weeks gestation because of complaints of bdominal pain. Bilateral theca lutein cysts ere found and haemoperitoneum caused by rupture of the right ovary Urinary gonadotrophin between and 5 million /24 hr A right oophorectomy was perf rmed. Because of the bleeding tear in the left cyst was sutured, lea ing the cyst intact and in situ. Microscopic examination of the excised ov ry disclosed many follicular cysts and marked lutei transformation of the ovary Fetal cardiac activity was determined by means of the ultrasonic Doppler fetal cardioscope. At 40 week *gestation dmitted in* labour Female infant 8 lb., 12 oz. Placenta normal on both gross and microscopic examination.

a case with this ovarian reaction in pregnancy *However in cases where the uterus is of normal* expected size according to the dates from the last menstrual period and with HCG and oestrogen values within the normal ranges for the gestational age It would be safe to resort to expectancy *This ovarian reaction seems* in many cases to b associated with conditions with high HCG excretion e g hydatidiform mole choriocarcinoma and multiple pregnancy However the administration of HCG alone to nonpregnant women does not give this ovarian reaction.

A very similar reaction in the ovaries sometimes appears during treatment of amenorrhoeic women with human FSH in combination with HCG It seems that some women are especially



Fig. [illegible] Microscopic picture. Cysts of follicular origin with varying degree of luteinization.

Table II *Hormone analysis*

L.M P beginning of December 1963. Exploratory laparotomy on March 3. Delivery on September 13

Date	HCG (IU/l)	Total oestrog. (mg/24 hours)	Pregnandiol (mg/24 hours)
[illegible]3 64	300 000		
4.3 64	300 000	7.5	
5.3 64	200 000	7 1	
6.3 64		11 8	
11 3 64	400 000	4.6	
13.3 64	600 000		
22.3.64	120 000	9 7	12.4
12.4 64	30 000	5 4	18.7
23.5 64	40 000	[illegible]	23.2
3.8.64	40 000	14 4	

sensitive and have some defect in their ovaries which gives the basis for this reaction.

It may be noted that in the reported cases of normal single pregnancy combined with bilateral multiple lutein cysts in the ovaries most women delivered a female infant.

REFERENCES

Baird, D Combined Textbook of Obstetrics and Gynaecology E. S. Livingstone Ltd. 1950.

Bergman, P Obst Gynec *21* 28 1963

Dowing, G C. Obst Gynec *18* 770, 1961

Girouard, D. P Barclay D L. & Collins, C. G Obst Gynec *3* 513 1964

Kesler K. F & Callagan, D A. Obst Gynec *29* 834 1967

Lerner A., Villanueva, C. & Tannhauser S. Amer J Obst Gynec *75* 203 1958.

Parker R. E. & Fisher E. L. Obst Gynec *23* 89 1964.

Rabinowitz, P JAMA *177* 509 1961

Rudolph, A. J & Barnett, R. V Obst Gynec *8* 293 1956.

Sarram, M. Obst Gynec *17* 366, 1961

Shettles, L. B. Obst Gynec *1* 330, 1963

V go O Sutrin. W Badea, L. & Pascu, F Zbl Gynaek *86* 805 1964

Watson, R. M & Demick, P E. Obst Gynec *14* 120 *1959*

Weigle E. H. & Thatcher A. H. Amer J Obst Gynec *70*. 1136, 1955

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ON RELATIONSHIP BETWEEN MATERNAL HEALTH AND INTRAUTERINE GROWTH OF THE FOETUS

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Abstract The relationship between maternal health and intrauterine growth of the foetus was studied. A prospective method of study was used and the series included 11 417 pregnant women. All infants of low birth weight and subgroup of growth retarded infants were compared with control group of normal weight infants. It became evident that the characteristics and complications of pregnancies resulting in infants of low birth eight differed from those of control series. It was also apparent that pregnancies resulting in growth retarded infants differed from controls in other respects than those resulting in premature infants as hole. In studying the causes of prematurity and in the clinical handling of the premature infants it is of utmost importance to be aware of the different categories of infants of low birth weight.

In 1961 the World Health Organization suggested that infants with a birth weight of 2 500 g or less should be called infants of low birth weight" rather than premature. The earlier accepted term prematurity" has been found inadequate for several purposes. Not all infants weighing 2 500 g or less are premature in the sense of being borne too early. In some cases the low birth weight is caused by retarded intrauterine growth of the foetus

Among the children with low birth weight two categories can thus be distinguished:

1 Truly premature infants, whose birth weight is low but ithin the limits accepted for a given gestational ge. The normal intrauterine growth of the foetus has been interrupted by premature onset f labour

Growth etarded infants, whose birth weight is lower than expected at given gestational ge. The intrauterine growth of the foetus has been retarded, resulting in small for dates or dysmature children, irrespective of whether or not pregnancy has been curtailed. As a rule intrauterine growth retardation is diagnosed if the birth weight of the child is more than two standard deviations below the mean for the duration of pregnancy calculated from the last menstrual period.

The term intrauterine growth retardation was originally introduced by Warkany et al., 1961 Various descriptive terms have since been applied to this condition such as chronic foetal distress (Gruenwald, 1963) and small for dates" (McDonald, 1965) During the last decade much interest has been shown in those babies whose birth weight is inappropriate for their gestational age. The obstetricians have studied the influence of antenatal care and different obstetrical complications on the intrauterine growth of the foetus. The paediatricians have focused their interest on neonatal complications and the further development of the small for dates infants.

Retarded intrauterine growth of the foetus may be caused by adverse factors in the intrauterine milieu. Genetic causes are probably of great importance. Ounsted (1965) has thus shown that siblings of small for dates babies have a statistically significant lower birth weight than normal, whereas siblings of prematurely born infants have a normal birth weight.

The present material was originally collected to study the relationship between maternal health and congenital malformations of the infants. It was considered worth while to use this series in an attempt to assess the abnormal features associated with the birth of child of low birth weight but especially of a growth retarded baby The aim of the study was to examine whether various fac

Table I. *Various disorders during pregnancy*

Morbid state of mother	Prematures		Small for dates		Controls	
	Number	Percentage	Number	Percentage	Number	Percentage
Anaemia (Hgb < 60 %)	56	10.8	11	8.9	974	9.5
Excess. vomiting	10	1.9	3	_4	81	0.8
Urinary infection	15	_9	3	_4	345	3 4
Cholelithiasis	2	0.4	—	—	76	0.7
Narcosis	1	0.2	—	—	—	—
Trauma or operation	9	1 7	1	0.8	285	_8
Threatened abortion	41	7.9	7	5 7	313	3.0
Placenta praevia	5	1.0	—	—	22	0._
Abruptio placentae	12	2.3	3	_4	3	—
Pregnancy toxaemia	58	11.3	19	15.3	5 4	5.1

tors associated with prematurity defined by weight alone also act in determining the intrauterine growth of the infant. The two groups were compared with a control series of babies weighing more than 2 500 g

We have preferred to retain the term "premature" for all infants of low birth weight. The subgroup of growth retarded infants who according to definition, weigh less than two standard deviations below the mean for the duration of pregnancy are called "small for dates"

Planning of the investigation

This prospective study includes all pregnant women seen at the Prenatal Care Centres of Gothenburg during the period 1954–1958. The patients at these centres come from a uniform cross section of all economic and social classes.

The planning of the investigation has been described earlier in detail (Hedberg et al., 1967). I summary every woma was interviewed at her first visit to the Centre. Any significant disease prior to pregnancy and the outcome of previous pregnancies wer noted on standard form. This special card was completed at each visit to the Centre and notes were made concerning accidents, diseases and exposure to contagious diseases during the actual pregnancy

The information obtained was coded for automatic data processing. In the statistical analysis of the differences obtained the χ test was employed.

MATERIAL AND METHODS

The case material includes 11 417 women who ited a Prenatal Care Centre in Gothenburg during pregnancy In 10 802 cases the pregnancy proceeded t the last trimester and the data on examination of mother and child were considered adequate In the remaining cases the pregnancy had generally terminated in abortion or the patient had moved y

All the children were examined by the paedia of the Clinic. In all cases of stillbirth and ne death post-mortem examinations were made at the l logical Laboratory of the hospital.

Of the total series, 513 children were prematu cording to the universally accepted definition i.e. _500 g or less. Of these infants of low birth weigh were classified as small for dates. The small for babies had a birth weight which was more tha standard deviations below the mean for the durati pregnancy calculated from the last menstrual p In calculating the birth weight in relation to gesta age we used standard curves produced by Engstr Sterky (1966). These curves were based on materi cluding all hospital deliveries in S eden during period July 1 1956 to June 30, 1957 The curves designed for both weights and lengths of newborn b and separately for boys and girls. All stillbirths, carriages, multiple births and cases involving tox were eliminated.

In the present series of small for dates babies those mothers were included whose date for the menstrual period was definitely known and in who uterine size and the time of the first foetal move was equivalent to the stated period of gestation. M births were not included in the series. Of stillborn in only those were included where the death of the had occurred immediat ly before or during the del

The control series consists of all mothers of t with a birth weight of more than 500 g

RESULTS

The incidence of small for dates among all pr ture infants is generally suggested to b betw _0 and 30 Differences in frequencies repo may be due to race social standard etc In present series the frequency of small for dat _4 of the premature infants.

Previous studies have demonstr ted a relat ship between maternal age and incidence of

maturity The lowest rates are reported for women in the age group 20–29 years with higher rates for younger and older women. It may thus be expected that the age of the mother is also of importance in the genesis of intrauterine growth retardation. In the present series there was no significant difference in the age distribution be tween mothers of small for dates babies and the control series. On the other hand difference in maternal age was found when comparing the total group of prematures with controls, with a higher proportion of younger and older women in the first group.

The obstetric history of mothers of small for dates babies differ from that of mothers of prema ture infants as a whole. Among mothers of small for dates babies there are more primigravidae than among the controls Comparing the total group of prematures with controls no such dif ference was found. Previous abortions, stillborn infants and earlier obstetric operations were found more commonly in the obstetric history of mothers f premature infants than of controls, whereas no such difference was found concerning mothers of small for dates babies.

Regarding the general health of the mothers before the index pregnancy we found no dif ference between the series f premature, small for dates and control infants. This holds true both for general medical and surgical diseases and for localized gynaecological disorders.

Most uthors have found that pregnancies resulting in children of low birth weight show a higher incidence of obstetric complications such as bacteriuria or urinary infections, bleeding during pregnancy acute toxaemia and premature separation of placenta. Data regarding obstetric complications in this study are set out in Table I

The number of cases are too small to allow statistical evaluation with regard to some complications With diagnostic methods available in 1954–1958 we found no increased incidence of urinary infections in mothers of premature infants or small for dates infants as compared with the control series. Bleeding during pregnancy was more common in pregnancies resulting in premature infants than among control but no such difference was found regarding small for dates babies

Toxaemia of pregnancy has been suggested as an important cause of retarded intrauterine foetal growth, owing to the changes in the placental function. But severe pregnancy toxaemia often necessitates early induction of labour and thus predisposes to birth of prematurely born infants. In the present series we found a significantly higher incidence of toxaemia among mothers of premature infants as a whole and among mothers of small for dates infants, as compared with controls. The difference was greater in the case of mothers of small for dates babies.

It is obvious that especially the long-standing and severe toxaemia of pregnancy causes extensive changes in the placenta resulting in placental insufficiency and growth retardation of the foetus. A pathological-anatomical examination of the placentas in our series has shown a significantly higher incidence of placental infarcts in all cases of prematurity and in small for dates babies as compared with controls.

We found no difference in sex distribution be tween the different groups of infants in our series. Congenital malformations were significantly more common among the premature infants as a whole and among small for dates infants as compared with the controls. Some types of congenital malformations such as acrania, microcephaly phocomelia by their nature result in a reduction of the birth weight of the infant.

We have tried to study the subsequent development of the children by means of information from the Children s Welfare Centres and later from the school medical officers. For many reasons this follow-up-study was difficult to perform and only about 20% of the cases could be fol lowed for more than 3 years after birth of the child. Even so we found a significantly higher incidence of mental disturbances among premature infants generally and among small for dates infants, as compared with the controls.

DISCUSSION

The clinical importance of a low birth weight is apparent. Infants of low birth weight show a high incidence of perinatal morbidity and mortality and the further development of the child is often impaired. In studying the causes of prematurity and in the clinical handling of the premature infants all infants of low birth weight were regarded merely as a uniform group. In the last decade, however it has become evident that among the

infants of low birth weight there exist different groups. In some of these infants the low birth weight is caused by premature onset of labour while in others the low birth weight is caused by retarded intrauterine growth. In studying the problems of prematurity it is of utmost importance to be aware of these different categories of premature children

In the present investigation we have studied the maternal health before and during the pregnancy in an attempt to find a relationship between maternal conditions and birth weight of the infant. We have studied the total group of infants of low birth weight and the subgroup of growth retarded infants separately. These two groups have been compared with a control group of normal weight infants. It became evident that the characteristics and complications of pregnancies resulting in infants of low birth weight were different from those of the control series. It was also apparent that mothers of small for dates infants differed from the controls in other respects than mothers of premature infants as a whole

Primiparity is significantly more common among mothers of small for dates infants than among controls It is a well known fact that the birth weight of the first born baby is lower than that of subsequent siblings. Consequently it seems reasonable that first born infants should be over represented in a series of small for dates infants. The cause is probably to be found in local factors relative to the local uterine milieu of the primigravida.

In contrast to parity the age of the mother seems to have no influence on the intrauterine growth of the foetus, nor does the health of the mother prior to pregnancy appear to be of any importance in this respect. The obstetric history of mothers of small for dates infants did not differ from that of controls. From the results of the investigation it seems more probable that high or low age of the mother as well as a history of earlier abortions and stillborn infants predisposes to premature delivery rather than to intrauterine growth retardation

Pregnancy toxaemia seems to be an important cause of intrauterine growth retardation. The extreme placental infarction associated with long-standing toxaemia results in placental insufficiency and undernourishment of the foetus. Early induction of labour is a common therapeutic measure in cases of severe pregnancy toxaemia an[d] so the incidence of prematurely born infants i[s] also high among toxaemic mothers.

Female infants are as a rule smaller than male[s] and consequently the female infants are usuall[y] overrepresented in earlier published series o[f] growth retarded infants. In the present study th[e] standard curves for birth weight in relation t[o] gestational age were made separately for boy[s] and girls. Using these curves no difference in se[x] was found between growth retarded infants an[d] controls.

Congenital malformations are common among infants of low birth weight. The low birth weigh[t] may be due to a premature onset of delivery. I[n] other cases the malformation per se is the caus[e] of a low birth weight but a growth retardation ma[y] also be part of the maldevelopment of the child.

Many authors who have studied large series of growth retarded infants agree that there are clinically several subgroups. Growth retarding factors, genetic or environmental, acting throughout the pregnancy will result in infants of low stature and low birth weight Placental insufficiency caused for instance by toxaemia, acting only during a short period of pregnancy will result in a baby of normal stature but of low birth weight. In these cases the low birth weight is mainly caused by undernourishment Gruenwald (1963) used the term chronic foetal distress, lasting for several months, where the foetus stopped growing before it had any panniculus adiposus and before its muscle mass was very great. The baby born following chronic foetal distress was of about normal external proportions because it stopped growing at the same time as it stopped gaining weight. Sub-acute foetal distress, on the other hand, is measured roughly in days. The baby is therefore of normal length but has lost weight and so looks long and thin.

Gentz & Sterky (1966) have suggested that in studying the small for dates infant not only the weight but also the length of the infant should be considered in relation to the duration of pregnancy In doing so they found three different categories of infants of low birth weight. the real premature infant, the infant of normal length but low birth weight and the infant of low birth weight and short stature The authors also gave examples of early and late symptomatology and of the prognosis for the three different categories

of infants. In the present investigation we tried to classify infants of low birth weight both according to weight and length. Unfortunately we had to give up the idea, as the groups were too small to allow statistical analysis.

REFERENCES

Engström, L. & Sterky G. Standardkurvor för vikt och längd hos nyfödda barn. Läkartidn 63 4922, 1966.

Gentz, J & Sterky G Förslag till ny klassifikation av nyfödda barn. Läkartidn 63 4909 1966.

Gruenwald, P Chronic fetal distress and placental insufficiency Biol Neonat 5 215 1963.

Hedberg, E., Holmdahl, K. & Pehrson, S.. On relationship between maternal health and congenital malformations. Acta Obstet Gynec Scand 46, 378, 1967

McDonald, A.. Retarded foetal growth. *In* Gestational age, size and maturity Clinics in Developmental Medicin, 19 14 (ed. M. Dawkins & B MacGregor). London, 1965

Ounsted, M.. Maternal constraint of foetal growth in man. Develop Med Child Neurol 7 479 1965

Warkany J Monroe, B. B. & Sutherland, B. S Intrauterine growth retardation. Am J Dis Child 102 249 1961.

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Acta Obstet Gynec Scand 49: 231–234 1970

OBSTETRICAL ANALGESIA IN NORWAY

Bjørn Lind

From the Department of Anaesthesia (Head: B. Lind, M.D.), Akershus Central Hospital, Nordbyhagen, Norway

Abstract. A random sample of 503 women from all parts of Norway who had given birth to a child during the last 24 months, were interviewed by the Scan-Gallup institution. Only 31% of the women thought they had received any kind of analgesia during stage 1 and 55% [illegible] been sutured. Nevertheless 80% were satisfied with the treatment and care given, and of the dissatisfied, 70% complained of lack of attention and only 17% of too little analgesia given.

During the last 3 or 4 years criticism has been focused on the service given to parturient women in Norwegian maternity hospitals. The purpose of this investigation was to find out how many of the mothers were displeased for one reason or another in order to achieve a basis for improvement.

METHODS AND MATERIAL

A random sample of 503 women from all parts of the country were interviewed by the Scan-Gallup institution. The women had all given birth to a child during the last 24 months. Caesarean sections and forceps deliveries were excluded. Table I shows the distribution of the material.

All Norwegian maternity hospitals also received a questionnaire to be filled in by the obstetrician, the surgeon or the midwife in charge. The answers were representative [illegible] % of all deliveries taking place in one year.

RESULTS AND DISCUSSION

When asked which part of labour was the most painful, 57% answered the first stage, 28% the second stage and 14% the suture. 17% described their pain as almost unbearable, 55% as severe and 8% as moderate. Among primigravidas there were 6% more who complained of almost unbearable pain than among the parous women.

Some of the mothers may not know which type of analgesia they have received, or if they have been given any analgesic at all. The question to be answered was: Did you receive a local analgesic, a pain-relieving drug by injection or an inhalation analgesic, or were you not given any analgesic at all?

Table IV shows the results. Two per cent said they received a local analgesic, 23% a general analgesic by injection and 6% a general analgesic by inhalation. 69% specified that they were not given any analgesic at all. The effect of the analgesic as judged by the mothers is shown in Table V. $^1/_3$ felt greatly relieved, $^1/_3$ had some help and $^1/_3$ did not notice any effect. With the small numbers in this series one could not detect any difference in the success of the different types of analgesics. Table VI shows that 54% of the women who described their pain as almost unbearable did not receive any analgesic at all, and 10% of these women maintained that they were in labour for more than 20 hours.

The suturing of episiotomy wounds or tears without any analgesics has been considered to be particularly rough and unnecessary. Out of 376 mothers who were sutured, 45% stated that they had received no analgesia. However, a local analgesic may in some cases have been injected before the episiotomy was performed and thus passed unnoticed, and in a few cases a couple of stitches may probably not have been more annoying than the injection of a local analgesic. $^3/_4$ of those who received an analgesic for the suturing reported good relief or some relief. The difference between the various types of analgesics is

Paper read at the 9th Congress of the Scandinavian Society of Anaesthesiologists, Bergen, Norway, June 1969.

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Hand-held ultra sound monitor hears foetal hearts as early as the 12th week



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Table IV shows the results. Two per cent said they received a local analgesic, 23% a general analgesic by injection and 6% a general analgesic by inhalation. 69% specified that they were not given any analgesic at all. The effect of the analgesic as judged by the mothers is shown in Table V. [illegible] felt greatly relieved, [illegible] had some help and [illegible] did not notice any effect. With the small numbers in this series one could not detect any difference in the success of the different types of analgesics. Table VI shows that 54% of the women who described their pain as almost unbearable did not receive any analgesic at all, and 10 of these women maintained that they were in labour for more than 20 hours.

The suturing of episiotomy wounds or tears without any analgesics has been considered to be particularly rough and unnecessary. Out of 376 mothers who were sutured, 45% stated that they had received no analgesia. However, a local analgesic may in some cases have been injected before the episiotomy was performed and thus passed unnoticed, and in a few cases a couple of stitches may probably not have been more annoying than the injection of a local analgesic. [illegible] of those who received an analgesic for the suturing reported good relief or some relief. The difference between the various types of analgesics is

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Table I *Distribution of the material*

	Obstetrical departments	Surgical depts.	Maternity homes	At home
% of 503 deliveries	64	22	13	1

Table II

Most painful part of delivery	% of mothers
Stage I	57
Stage II	28
Suture	14
Uncertai	2

Table III

Degree of pain	% of mothers
Almost unbearable	17
Severe	55
Moderate	28

Table IV

Pain relieving methods	% of mothers
Local analgesic	2
Drug by injection	23
Inhalation analgesic	6
No analgesic	69

small, local infiltration probably being the most effective and topical analgesia the least.

According to the information collected from the maternity hospitals, the probability of being admitted to a ward where analgesia is never given, is remote Analgesia has therefore been withheld either because of contraindications or because it has not been considered necessary (Table VIII)

It is well known that to be left alone exerts a great stress upon a woman in labour Table IX shows that 31 % reported somebody being present all the time, 10 % half the time, 54 % now and then and 5 % maintain they were left completely alone during their labour Of those present, 76 % were midwives. Many mothers wish their husbands to be with them during their labour In this series this took place only in 6 % of the cases. When questioned 41 % of the remainder answered th[at] they had wanted their husbands present. Co[n]sidering the shortage of doctors, midwives an[d] nurses in Norway and the great demand amon[g] the mothers to have their husbands present, th[is] should be arranged more often.

The recognition of the importance of ment[al] and physical training for labour has increased i[n] Norway In this series 29 % of the women ha[d] received some information about the course o[f] labour and been taught how to behave in order t[o] reduce the pain. 91 % declared that this informa[tion] had been of help to them. This is the highes[t] degree of success of any of the procedures i[n] this survey

Table V

Pain relief	% of mothers having received analgesics
Good	33
Moderate	38
No effect	29
Total	100
Number questioned	153

Table VI

Pain relieving methods	Degree of pain % of mothers Moderate	Severe	Almost unbearable
Local	1	3	2
Drug by injection	14	23	37
Inhalation analgesic	2	7	7
No analgesic	83	67	54
Total	100	100	100
Number questioned	140	277	86

Table VII

Pain relieving method	% of mothers sutured
Spray	34
Local	15
Inhalation analgesic	6
None	45
Total	100
Number questioned	376

It has been emphasized that the delivery and the recollection of the event is of great importance in determining the attitude of the mother to her child. Some women maintain that the reminiscences of the delivery torment them as night mares. Table X shows that this is the case in 6% of the women questioned. The incidence is lower than suggested by the lay press, but high enough considering that this event ought to stand as a climax in their life. The incidence did not vary with the place of birth, the age of the women or whether it was the first or later deliveries.

Looking closer at these 6% we see that they have had labours f longer duration and more severe pain than the average in the series, and when asked, what more could have been done for

Table VIII *Analgesia in Norwegian labour wards*

Method	Analgesia obtainable % of 40 000 deliveries
Stage I	
Paracervical block	7
Lumbar epidural block	1
Pethidine	55
Diazepam	80
Trilene	25
N_2O	12
No analgesia	3
Stage II	
Spray	40
Local infiltration	44
Inhalation analgesia	16
No analgesia	5

Table IX

Someone present	of mothers
All the time	31
Half the time	10
Occasionally	54
No one present	5

Table X

Reminiscence of delivery	% of mothers
With pleasure	33
A painful, but happy event	60
Recollection torments me	6
Uncertain	1

Table XI

Degree of pain	% of mothers: Recollection torments me	Total material
Almost unbearable	58	17
Severe	42	55
Moderate	0	28
Duration of labour		
0–2 hours	6	17
3–19 hours	62	69
> 20 hours	32	15
Total	100	101
Number questioned	31	503

Table XII

Satisfied with treatment and care	Total material (%)	Someone present: All the time ( )	Half the time (%)	Occasionally (%)	None present (%)
Yes	80	94	92	73	59
No	20	6	8	27	41
Total	100	100	100	100	100
Number questioned	503	154	51	271	27

them, /a requested more attention, / mor analgesics and 1/ some other sort of help.

With such a low incidence of obstetrical analgesia offered and so little attention given to the mother, it is fair to ask: Does a relation f confidence exist between the mothers and the mater nity hospitals in Norway? The following question was therefore asked. Were you satisfied with the treatment and care you received during your labour and delivery? W notice that 80% of the mothers in spite of all were satisfied with the service given, and moreover more than 90% were happy if someone had been present when required.

Table XII shows that of these 20% who were not satisfied, we find that 70% complained of lack of attention, and only 17% thought that too little analgesia was given. One may ask then: Is there a need for more analgesics when 80% of the mothers accept the conditions as they are and only 17% of the remainder demand more

Table XIII

Complaints	% of dissatisfied
Lack of attention	70
More analgesic	17
Analgesic when suturing	5
Other complaints	25
Total	117
Number questioned	99

Table XIV

Better service desirable	% of obstetricians or midwives
Yes	66
No	25
Uncertain	9
Total	100
Number questioned	88

analgesia? I do not think one should feel content with these statements. The mothers are apt to compare their experiences with descriptions given by their friends. Few have given birth to children in places where more analgesics are offered

Let us therefore finally see how the obstetricians and midwives feel about this matter 66 % of those who have returned the questionnaire expressed the opinion that better service would be desirable Of the improvements proposed about $^1/_2$ suggested that a better service required more obstetricians and/or midwives, whereas 88 % stressed the importance of better knowledge and training in obstetrical analgesia. This shows that most obstetricians feel incompetent in this field and want to make themselves more familiar with it. I do suggest that this applies also for anaesthetists.

CONCLUSIONS

1 The mothers should not be left alone The presence of their husband would be a great comfort to many and should be encouraged.

2. Almost $^1/_2$ of the mothers have had the advantage of some mental and physical training for labour 91 % of them claim that this was of help Courses which give the mothers some knowledge about the delivery and instruction in how to lessen the ordeal of pain seem worthwhile.

3 Too many mothers had received little or no analgesia. The analgesics given were more or less successful in $^2/_3$ of the cases irrespective of the type The methods should therefore be chosen according to the skill and experience of the obstetrician, anaesthetist or midwife. The more elaborate methods belong to the obstetrical departments, the easier ones to smaller lying-in hospitals.

4 It is noteworthy that in spite of obvious shortcomings, 80 % of the mothers have confidence in Norwegian maternity hospitals.

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CYTOGENETIC INVESTIGATIONS IN MALE INFERTILITY

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Abstract Sex-chromatin and chromosomal investigations were carried out on 98 men, who were examined because of infertility They all had severely impaired or totally absent fertility as evaluated by seminal analyses Six were sex-chromatin positive and had 47,XXY chromosome complement Furthermore one had 47,XYY complement. This patient as well as the other 91 were chromatin-negative In another selection of hypogonadal men, both sex-chromatin positive and sex-chromatin negative patients with abnormal chromosome complements were found. It is therefore concluded that chromosomal abnormalities are important aetiological factors in male infertility Chromosome analyses as well as sex-chromatin analysis is thus necessary in the investigation of male infertility

Ten to 15% of all marriages in Europe and the USA are usually estimated to be infertile. The causes of the sterility are supposedly located slightly more frequently in the woman than in the man. Hammen (1944) found that the husband usually had an important role in the infertility which was often caused by more than one factor

Infertility in the male may have many causes. These will not be discussed systematically here and the reader is referred to such authors as Hammen (1944) and Williams (1968).

The degree of infertility in the male is usually estimated on the basis of seminal analyses. Preferably more than one analysis should be carried out but this method is difficult to evaluate. Absolute sterility should only be diagnosed in the case of aspermia, as discussed for example by Johnsen (1962) Investigation of the histology of the testis and hormone analyses (especially an investigation of the function of the adrenal cortex and the gonad i.e. fractionated 17-ketosteroids and gonadotrophin investigations) are significant in the evaluation of the fertility A general clinical examination is of course necessary—too

As it may be presumed that more insight into male infertility and into the significance of the spermiogram may be achieved through correlated investigations of sperm, testis histology meiotic and mitotic chromosomes, we have therefore begun such studies.

It is the purpose of this paper to publish the results of investigations of sex chromatin and mitotic chromosomes in selected subfertile men.

MATERIAL

We selected 98 men, referred because of infertility and who were found by seminal analyses to have aspermia or severe impairment of their fertility Only those who were willing to take part in all the planned investigations were included. As the patients were selected before being referred to us, we could not ensure that all such patients were included in the material presented here.

Seminal analyses as well as sex-chromatin examination of buccal smears and chromosome analysis of lymphocytes from peripheral blood were carried out on all patients. Ninety-five also had testicular biopsies taken (3 patients had undescended testes)

The seminal analysis was carried out according to the methods of Hammen (1944) On an average each patient had three such analyses, but in some cases only one was carried out, namely when the patient had had seminal analysis previously with identical results at other laboratories.

We classify the ejaculates routinely according to their quality in the following groups (I) normal fertility (II)

Table I

0 (Aspermia)	25
IV A	15
IV B	4
IV C	14
V A	12
V B	1
V C	7
Total (I II III)	98

slightly impaired fertility (III) moderately impaired fertility (IV) severely impaired fertility (V) very severely impaired fertility (0) aspermia (cf. Hammen, 1944).

In the present series only patients from the last three groups were included.

In Table I the material is divided according to the classification, but the quality groups are further subdivided as follows. (A) the main criterion is that the number of abnormal sperm heads exceeds 65% even if all the cases at the same time have oligo-astheno-spermia, (B) the main criterion is that the number of sperms is less than mill. per ml, even if all cases at the same time have terato- (abnormal morphology) astheno- (abnormal motility) spermia, (C) the main criterion is asthenospermia, even if practically all cases at the same time have terato-oligospermia.

Cells for sex-chromatin examination were stained with haematoxylin and t least one hundred undamaged vesicular nuclei were counted.

The chromosome analysis was made by a modification of the technique of Moorhead et al. (1960). At least ten cells, but usually more, in metaphase were counted and structural analysis was done on at least three metaphases after microphotography (Philip 1968)

RESULTS

Six of the 98 men were sex-chromatin positive the other 92 were sex-chromatin negative. By chromosomal analysis the sex-chromatin positive men were found to have 47 chromosomes and an XXY sex chromosome complement. One of the sex-chromatin negative men had 47 chromosomes and an XYY sex chromosome complement. Another sex-chromatin negative patient had an abnormal Y chromosome which was larger than the other chromosomes in group 21–22, and in several cells it appeared almost metacentric (Fig. 1). All the other patients had normal numerical and structural cytogenetic results.

The investigations of the histology of the testis will be published elsewhere. It should be noted, however that in 1 patient with 47 chromosomes and an XXY sex chromosome complement, spermatogenesis was found and examination of meiotic chromosomes was possible (Skakkebæk et al 1969). Due to the lack of knowledge about the fertility of men with XYY complements, the result of the examination of the histology of the testis of the patient with this chromosome complement will be published separately (Skakkebæk et al. in press).

DISCUSSION

Chromosomal abnormalities may be the cause of infertility in men as well as in women (cf Philip

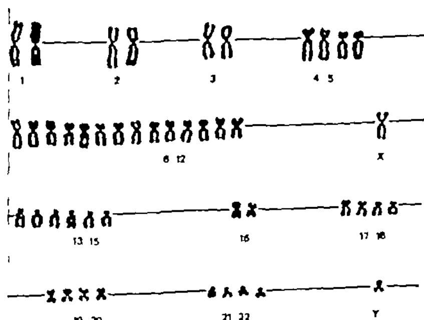


Fig 1 Karyotype of sex-chromatin negative male with large in many cells almost metacentric, Y chromosome



Fig. 2. Karyotype of sex-chromatin negative male with 45 chromosomes and an XY sex chromosome complement and translocation between two D chromosomes.

Selo & Trolle, 1965). The frequency of such abnormalities in patients complaining of infertility is very difficult to evaluate because all material, including the present, is preselected from more or less unknown criteria.

The correlation between sex-chromatin anomalies and sterility in men has already been investigated in 1957 by Ferguson-Smith. He made sex chromatin investigations on men with impaired fertility as evaluated from seminal analyses. Of 758 male patients who had seminal analyses because of infertility 50 had aspermia and 76 had less than 1 mill. sperms per ml. 91 of these 126 men, who were classified as having severely impaired fertility had sex-chromatin analyses: of these ten had sex-chromatin positive cells, six had aspermia and four extremely severe oligospermia).

Kjessler (1963, 1966) found about 16% sex chromatin positive males in a series of Swedish subfertile men with less than 1 mill. sperms per ml.

The high frequency of individuals with sex chromatin positive Klinefelter's syndrome among infertile men may now be understood, because the frequency of Klinefelter's syndrome is estimated at about 2 per 1 000 living newborn male babies. Although confident figures are difficult to obtain, some material is now available. Maclean et al. (1961) found 9 out of 3 000 examined newborn male babies to be sex-chromatin positive. These nine had either XXY chromosome complements or complements which were mosaics including cells with XXY. From other material available four in 1 332 (Walzer & Gerald, 1969) and one in 1 066 newborn males (Sergovich et al., 1969) had the XXY sex chromosome complement.

The significance of sex-chromatin as well as chromosome investigation of these patients is obvious, because groups of infertile men and also normal populations hold individuals with chromosomal abnormalities, which are not accompanied by sex-chromatin abnormalities. In this investigation the patient with the 47,XYY complement was thus chromatin-negative. In Kjessler's investigation 10 patients had abnormal chromosomes and only four of these were sex-chromatin positive. The others had either sex chromosome or autosomal anomalies and were chromatin-negative.

The same is illustrated by another investigation carried out by us. Among 169 men from the study section for male hypogonadism, two with chromatin-negative chromosomal abnormalities were found, although this group was not systematically investigated with regard to chromosomal abnormalities, but only for sex-chromatin abnormalities. One of the chromatin-negative patients had partial spermatogenic arrest between the spermatocyte and the spermatid-phase. He therefore had a chromosome analysis and was found to have a translocation between two chromosomes in the 13–15 group (Fig. 2). The second, who had a chromosome analysis, because of very small testes,



Fig 3 Karyotype of sex-chromatin negative male with 46 chromosomes and a presumably deleted Y chromosome

had 45 chromosomes plus a fragment, which for other reasons was interpreted as a deleted Y chromosome (Fig. 3)

The frequent finding of infertile, sex-chromatin negative men has also been confirmed by de la Chapelle & Hortling (1963) and by McIlree et al (1966 *a* and *b*)

Chromosomal abnormalities are thus important aetiological factors in male infertility at least in men with abnormal spermiograms. Whether such abnormalities are found in infertile men with normal sperm is much less certain Stenchever et al (1969) found no chromosomal abnormalities among 25 married couples with primary and 7 with secondary sterility These 64 individuals were selected for chromosomal analysis because all other investigations had proved normal

Apparently normal spermiograms do not, however exclude chromosomal abnormalities Kjessler (1966) found abnormal chromosomes in patients who had up to 80 mill. sperms per ml and with less than 30 % sperms with abnormal morphology in their ejaculates. In our series 1 patient with a 47,XYY chromosome complement had 3 mill sperms per ml

Our material was selected for sterility De la Chapelle & Hortling (1963) selected a group of patients who consulted endocrinologists because of impaired or supposedly impaired sexual development or function. Thirty four of their patients showed clinical symptoms of hypogonadism and one half of these had abnormal chromosome complements. It is noteworthy that they found that some patients with cryptorchidism had abnormal chromosomes.

A perusal of the literature on abnormal Y chromosomes including abnormally long ones, seems to show that Y chromosomes abnormalities are so frequent, that any pathogenetic significance regarding infertility cannot be attached to them. Apparently abnormally long Y chromosomes were found in several of our patients and at least 1 patient with an almost metacentric Y chromosome in many cells was also found. Because sex chromosome abnormalities are not necessarily accompanied by infertility or sexual abnormalities (Sohval, 1963), it becomes even more difficult to evaluate the significance of such findings.

It may finally be mentioned that chromosomal abnormalities in men and women may hamper fertility not only by preventing conception, but also because of an increased tendency to abortion. It is however doubtful whether this has any quantitative importance. Singh (1966) thus investigated 22 couples in whom the female partner had had an abortion with abnormal chromosomal complements. All these individuals had normal chromosomes and this has been confirmed by Shaw (cit. Stenchever et al 1969) Bishun & Morton (1968) also found normal chromosomes in 27 women who

had had at least 2 spontaneous abortions. Pergament et al (1968) found only one translocation (between two D chromosomes) among 39 couples and 4 women who had had at least two spontaneous abortions. Many of these also had living children or had had stillbirths. These authors also found many structural variations, which at present (Court Brown et al., 1966) are supposed to be of no pathological significance.

REFERENCES

Bishun, N. P. & Morton, W. R. M., J Obstet Gynaec Brit Commw *75* 66, 1968.

La Chapelle, A. de & Hortling, H. Acta Endocr *44* 165, 1963.

Court Brown, W. M., Buckton, K. E., Jacobs, P. Tough, I. M., Kuenssberg, E. V. & Knox, J. D. E. *Eugenics* Lab. Mem. XLII. Cambridge University press 1966.

Ferguson-Smith, M. A., Lennox, B., Mack, W. S. & Stewart, J. S. S. Lancet *2* 167 1957.

Hammen, R. Studies on impaired fertility in man with special reference to the male (thesis). Copenhagen, 1944.

Johnsen, S. G. Acta Endocr *40*: Suppl. 66, 1962.

Kjessler, B. Lancet *2* 493, 1965.

— Monographs in human Genetics *2*. Karger, Basel, 1966.

Maclean, N. Harnden, D. G. & Court Brown, W. M. Lancet *2* 406, 1961.

McIlree, M. E. Tulloch, W. S. & Newsam, J. E. Lancet *1* 679 1966.

McIlree, M. E. Price, W. H. Court Brown, W. M. Selby T. W. Newsam, J. E. & Maclean, N. Lancet *2* 69 1966.

Moorhead, P. S. Nowell, P. C., Mellman, W. J. Batipps, D. M. & Hungerford, D. A. Exp Cell Res *20* 613, 1960.

Pergament, E., Kadotani, T. & Sato, H. Amer J Obstet Gynec *100*: 912, 1968.

Philip, J. Lancet *1* 209 1968.

Philip, J. Sele, V. & Trolle, D. Fertil Steril *16*. 795 1965.

Sergovich, F. Valentine, G. H. Chen, A. T. L., Kinch, R. A. H. & Smout, M. S. New Engl J Med *280* 851, 1969.

Singh, R. P. Rubinoff, A. & Carr, D. H. Lancet *2* 445 1966.

Skakkebæk, N. E., Philip, J. Hammen, R., Nielsen, J. Yde, H. Perboll, O. & Mikkelsen, M., Fertil Steril. In press.

Skakkebæk, N. E., Philip, J. & Hammen, R. Nature *221* 1075, 1969.

Sokval, A. R. Fertil Steril *14* 180, 1963.

Stenchever, M. A., MacIntyre, M. N., Jarvis, J. A. & Hempel, J. M. Obstet Gynec *33* 380, 1969.

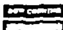
Walzer, S. Breau, G. & Gerald, P. S. J Pediat *74* 438, 1969.

Williams, R. H. Textbook of Endocrinology. Saunders, Philadelphia, 1968.

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HUMAN PLACENTAL TRANSFER OF AN ANTIFIBRINOLYTIC AGENT (AMCA)

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Abstract A fibrinolytic inhibitor AMCA (trans p-aminomethyl cyclohexane carboxylic acid) was given in a dose of 0.01 g/kg bodyweight to 12 mothers about to be delivered by Caesarean section. Immediately after delivery the concentration of AMCA was determined in the maternal blood and in cord blood. AMCA was determined by a chemical method based on high voltage paper electrophoresis and photometric determination of the ninhydrin complex. It was found that AMCA passes through the placenta and that the concentration of the drug in the cord blood can be fairly high (4–31 µg per ml). The possible value of prophylaxis of the foetus with AMCA by the maternal route to check fibrinolytic bleedings (pulmonary or intracranial) sustained during premature delivery is discussed.

We have long been interested in the effect of antifibrinolytic agents in the treatment of fibrinolytic haemorrhages. The first drug we studied was EACA (epsilonaminocaproic acid) (Nilsson, Sjoerdsma & Waldenström, 1960; Nilsson, Björkman & Andersson, 1961, 1966). More recently we have focused our interest on AMCA (tranexamic acid, trans p-aminomethyl cyclohexane carboxylic acid) (Andersson et al., 1965). Melander et al. (1965) and Andersson et al. (1968) have described chemical methods (based on high voltage paper electrophoresis and photometric determination of the ninhydrin complex) for assay not only of blood levels, but also of tissue levels of EACA and AMCA. As an inhibitor AMCA has certain advantages over EACA. It is about 10 times more potent and its side effects are both milder and less frequent.

One of the indications for the use of antifibrinolytic agents is fibrinolytic bleeding in association with delivery. We therefore considered it of interest to find out whether such agents pass through the placenta. Since AMCA must at present be considered the antifibrinolytic drug of choice, we gave it to 1 women just about to be delivered by Caesarean section. The concentration of AMCA was determined in maternal and in umbilical cord blood.

MATERIAL AND METHODS

AMCA. A sterile aqueous solution Cyklokapron® (produced and supplied by AB Kabi, Stockholm, Sweden) containing 0.1 g/ml was used.

Clinical Material. The clinical material consisted of 12 healthy women in the last month of pregnancy and about to be delivered by Caesarean section because of narrow pelvis or similar conditions. Just before operation blood samples were drawn from the patients who were immediately afterwards given an intravenous injection of 0.01 g of AMCA per kg bodyweight within a period of 5–10 min. After delivery (about 10–20 min after the end of injection) blood samples for determination of AMCA were obtained from the mother and from the umbilical cord of the infant. The samples were allowed to clot after which they were centrifuged and the serum was stored at −20°C until used.

Assay of AMCA. The method used for identification and assay of AMCA in serum has been described in detail by Andersson et al. (1968). It is based on high voltage paper electrophoresis and photometric determination of the ninhydrin complex.

RESULTS AND COMMENTS

It is clear from the table that the concentration of AMCA in the maternal sera following injection of the drug in a dose of 0.01 g per kg bodyweight varied from 10 to 53 µg per ml, a range in good agreement with that reported by Andersson et al (1965 and 1968). Serum samples from the full-

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URINARY EXCRETION OF OESTROGENS AND THE OESTROGENIC EFFECT IN VAGINAL SMEARS IN POST-MENOPAUSAL WOMEN WITH UTERINE BLEEDING

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Abstract. A series consisting of 145 post-menopausal women with uterine bleeding and a control group of 55 post-menopausal women without this symptom were investigated. The urinary excretion of oestrone, oestradiol and oestriol was measured on three consecutive days. The oestrogenic effect in vaginal smears was determined and the endometrium was histologically investigated. In those patients with uterine bleeding who showed an oestrogenic effect in the endometrium or an endometrial polyp, the urinary excretion of oestrone, oestradiol and oestriol and the oestrogenic effect in the vaginal smear were clearly higher than in the control group, although overlapping occurred. In those patients in the bleeding group who had atrophic or slightly proliferative endometrium or endometrial carcinoma, the urinary oestrogen excretion was low and the oestrogenic effect in the vaginal smear was poorly developed, and did not differ from the corresponding values in the control group. Of the various urinary oestrogen values (oestrone, oestradiol, oestriol and the sum of these) the total value was found to correlate most obviously with an endometrial oestrogenic effect. A positive correlation was also observed between an oestrogenic effect in the vaginal smear and an endometrial oestrogenic effect.

The post-menopausal endometrium does not always show a simple atrophic pattern; it often exhibits an oestrogen effect varying in degree (Novak & Richardson, 1941; Novak, 1944; Fahlund & Broders, 1946; Kottmeier, 1947; Davies & Williams, 1957; Lehto & Kantonen, 1957; Parks et al., 1958; Noer, 1961; Procopé, 1968). These endometrial changes may result in uterine bleeding. Post-menopausal uterine bleeding may however also be due to atrophic changes, a polyp or a malignant process.

Increased oestrogenic activity in vaginal smears in cases of post-menopausal bleeding has been reported by Lajos et al. (1963), and Frampton (1966).

Since the development of chemical methods of measuring urinary oestrogens (oestrone, oestradiol, oestriol), the reliability of oestrogen determinations has increased and it has been proved that these three "classical" oestrogens are present not only in the urine of fertile women but also in the urine of post-menopausal women (Brown, 1955, 1958; McBride, 1957; Breuer et al., 1957; Lyngbye & Mogensen, 1961; Brown & Matthew, 1962; Nissen-Meyer & Sanner, 1963; Grönroos, 1965; Furuhjelm, 1966; Procopé, 1968).

In cases suspected of increased oestrogen production it is advisable not only to investigate the endometrium but also to determine the oestrogenic effect in vaginal smears and the urinary oestrogen excretion.

MATERIAL

The series consisted of 145 post-menopausal women with uterine bleeding. They were at least 45 years old and the time lapse since the last menstruation was at least one year. The control group consisted of 55 post-menopausal women, who likewise were at least 45 years old and had had their last menstruation at least one year previously. In these cases there had been no uterine bleeding. The mean age in the bleeding group was 66.5 years, the mean menopausal age was 49.3 years and the mean time lapse since the menopause was 10.5 years. The corresponding values in the control group were 62.8 years, 49.6 years and 13.[illegible] years (Table I).

The liver function was checked by determining serum bilirubin, alkaline phosphatase, aspartate transaminase (GOT), alanine transaminase (GPT) and by the thymol turbidity test. Blood clotting was assessed by determina-

Table I

Case	Maternal blood serum		Cord serum	
	Time after end of inf. (min)	Concentration of AMCA (µg/ml)	Volume (ml)	Concentration of AMCA (µg/ml)
R. T	15	28	4.2	29
M M	15	37	1 8	<4
I E.	25	14	2.5	12
B N	15	26	1.3	<6
L N	10	30	2.7	22
I S.	15	53	3.5	31
A. B.	10	10	3.6	7
M J	8	18	1 4	26
E. J	8	27	8.8	4
K. J	18	21	3.8	14
F L.	5	24	1.5	13
G M	10	78	4.2	9

term infants cord blood contained AMCA in a concentration of 4 to 31 µg per ml

It is thus obvious that when the antifibrinolytic drug AMCA, is administered to women in the last trimester of pregnancy it passes through the placenta. The half life of AMCA in serum is short, about 1–2 hours (Andersson et al., 1965) Newborn babies have a high fibrinolytic activity in the blood (Markarian et al., 1967 Ekelund, Hedner & Nilsson, 1969) Whether suppression of this activity during the first few hours of life has any untoward effect on the normal infant is not known with certainty but we have often used AMCA in connection with delivery and never observed any side effects in the infants.

Our finding that it is possible to suppress the fibrinolytic activity in the new-born by medication of the mother offers interesting aspects of early treatment of pulmonary and intracranial haemorrhages sustained by the foetus during its passage through the birth-canal. Such haemorrhages may be fatal, especially in premature babies. The level of pulmonary plasminogen activator in the newborn is high (Ambrus et al., 1965) and this may account for the most severe haemorrhagic manifestations occurring in the lungs. Intracranial haemorrhages are most often initiated by vascular rupture but owing to the relatively poor coagulability of the blood in newborns, it might be wise to delay fibrinolysis, a measure proposed and used with some success in the treatment of subarachnoid haemorrhages (Mullan & Dawley 1968 Norlén & Thulin, 1968) In imminent premature labour the foetus could be given AMCA prophylactically by administration of the drug to the mother i e a route long used for prophylactic therapy with vitamin-K to decrease bleeding episodes in newborn babies. A controlled clinical trial would show the benefits and drawbacks of such prophylaxis with AMCA.

ACKNOWLEDGEMENT

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REFERENCES

Ambrus, C. M., Weintraub, D H., Niswander K. R. & Ambrus, J L., Pediatrics 35 91, 1965
Andersson, L., Nilsson, I. M., Colleen, S., Granstrand, B. & Melander B., Ann NY Acad Sci 146, 642, 1968.
Andersson, L., Nilsson, I. M Nilehn, J E., Hedner U Granstrand, B. & Melander B., Scand J Haemat 2 230, 1965
Ekelund, H., Hedner U & Nilsson, I. M., Acta Paediat. In press 1969
Markarian, M Githens, J H., Jackson, J J Bannon, A. E., Lindley A., Rosenblut, E., Martorell, R. & Lubchenco, L. O., Am J Dis Child 113 312, 1967
Melander B Gliniecki, G., Granstrand, B. & Hanshoff, G., Acta Pharmacol (Kbh) 340, 1965
Mullan, S. & Dawley J J Neurosurg 3 1 1968
Nilsson, I. M Andersson, L. & Bjorkman, S. E. Acta Med Scand. Suppl. 448, 1966.
Nilsson, I. M Björkman, S. E. & Andersson, L., Acta Med Scand 170 487 1961.
Nilsson, I. M Sjoerdsma, A. & Waldenström, J Lancet I 1322, 1960
Norlén, G & Thulin, C. A. Läkartidn 65 2910, 1968.

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Table II. *Histological structure of the endometrium, no. of cases, urinary excretion of oestrogens and mean KI and EI in the bleeding group*

The statistical significance, when the urinary excretion of total oestrogens and mean values of KI and EI in vaginal smear in the bleeding group is compared with the corresponding values in the control group, is indicated (Wilcoxon test). Oestrogen values and mean KI and EI values in brackets indicate range. The symbol means statistically insignificant

Histological structure of the endometrium	No. of cases	Urinary excretion of oestrogens (μg/24 hr): Oestrone	Oestradiol	Oestriol	Total oestrogens	Statistical significance (P)	KI and EI in vaginal smear (mean value)	Statistical significance (P)
Atrophic endometrium	33	M 1.4 (0.2–9.3)	M 0.9 (0.0–5.3)	M 6.0 (2.0–33.9)	M 8.2 (2.7–36.3)		M 7.2 (0–30)	
Slightly proliferative endometrium	8	M 1.7 (0.9–4.1)	M 0.6 (0.3–1.1)	M 7.1 (3.6–10.2)	M 8.4 (5.1–15.1)		M 9.2 (0–32)	
Proliferative endometrium	12	M 3.0 (0.4–7.3)	M 1.8 (0.2–3.5)	M 7.9 (5.0–19.4)	M 10.0 (6.3–23.8)	<0.02	M 32.2 (15–42)	<0.001
Hyperplasia	16	M 4.2 (0.6–22.8)	M 1.3 (0.2–11.6)	M 9.4 (3.0–25.4)	M 16.1 (8.3–49.2)	<0.001	M 25.5 (12–61)	0.001
Cystic glandular hyperplasia	20	M 4.1 (0.4–30.5)	M 2.9 (0.0–10.6)	M 12.6 (4.1–51.8)	M 18.9 (7.1–80.3)	<0.001	M 35.5 (15–70)	<0.001
Endometrial polyp	8	M 2.0 (1.4–62.7)	M 2.1 (1.0–10.9)	M 6.3 (2.4–25.6)	M 11.8 (6.2–99.2)		M 9.[illegible] (0–39)	
Endometrial polyp, atrophic endometrium	6	M 2.5 (0.6–3.6)	M 1.7 (0.0–4.1)	M 8.4 (5.0–15.0)	M 12.5 (5.6–19.5)		M 10.5 (0–19)	
Endometrial polyp, proliferative endometrium	5	M 2.1 (1.3–5.1)	M 1.1 (0.7–2.8)	M 10.9 (4.2–12.5)	M 13.8 (6.4–19.7)	0.001	M 22.2 (10–36)	<0.001
Endometrial polyp hyperplasia	5	M 6.3 (0.2–10.3)	M 1.6 (0.0–3.7)	M 12.5 (3.8–33.8)	M 17.5 (4.3–47.0)		M 25.5 (12–39)	
Endometrial polyp, cystic glandular hyperplasia	5	M 2.1 (0.4–11.3)	M 3.0 (0.0–4.2)	M 6.3 (3.0–16.2)	M 11.3 (6.3–31.3)		M 45.5 (20–65)	
Cervical polyp, atrophic endometrium	7	M 1.7 (1.0–3.2)	M 0.5 (0.3–2.5)	M 7.6 (4.7–17.6)	M 9.4 (6.8–21.1)		M 8.8 (0–21)	
Cervical polyp hyperplasia	5	M 4.4 (2.3–12.1)	M 2.2 (0.9–4.9)	M 12.5 (6.5–23.5)	M 17.5 (9.9–39.6)	<0.01	M 45.5 (18–64)	
Secretory endometrium	1	25.8	8.1	15.7	49.6		42	
Endometrial carcinoma	14	M 1.6 (0.2–3.5)	M 0.8 (0.2–1.4)	M 8.4 (3.6–10.7)	M 11.6 (2.4–13.6)		M 13 (0–21)	
Total	145	M 2.3 (0.2–42.7)	M 1.2 (0.0–11.4)	M 8.1 (1.3–51.8)	M 11.6 (2.7–99.2)		M 15.7 (0–70)	

the bleeding group, and the mean lapse of time since the menopause was somewhat longer.

The median values and ranges of the urinary excretion of oestrone, oestradiol, oestriol and the sum of these, and the median values and ranges of the mean KI and EI in the vaginal smear are shown in Tables II and III. Table II also shows the statistical significance (Wilcoxon test) of the difference between the urinary excretion of total oestrogens and the mean KI and EI in the patients with different histological pictures in the endometrium in the bleeding group and the patients in the control group. The values for the urinary excretion of oestrone, oestradiol and oestriol and the oestrogenic effect in the vaginal smear were low in the bleeding patients showing atrophic endometrium except in one case (total urinary oestrogens 36.3 μg/24 h, mean KI and EI 37). This patient was 52 years old and the time lapse since the last menstruation was only one year. Low values for urinary oestrogens were also noted in the bleeding patients showing slightly proliferative endometrium or endometrial carcinoma. The urinary oestrogen excretion and the

Table I. *Histological structure of the endometrium including cervical polyps no of cases, mean age and mean years after the menopause*

Histological structure of the endometrium	No. of cases	%	Mean age (years)	Mean years after the menopause
Bleeding group				
Atrophic endometrium	33	22.8	63.0	14.0
Slightly proliferative endometrium	8	5.5	55.6	4 8
Proliferative endometrium	12	8.3	59 6	8.0
Hyperplasia	16	11.0	55.3	5 0
Cystic glandular hyperplasia	20	13 8	58.3	8.3
Endometrial polyp	8	5.5	58.8	9 1
Endometrial polyp + atrophic endometrium	6	4 1	65.8	13.9
Endometrial polyp + proliferative endometrium	5	3 4	57.5	8 4
Endometrial polyp + hyperplasia	5	3 4	64.5	17.0
Endometrial polyp + cystic glandular hyperplasia	5	3 4	57.5	8.3
Cervical polyp + atrophic endometrium	7	4.8	67.5	17 6
Cervical polyp + hyperplasia	5	3 4	61.5	9.0
Secretory endometrium	1	0.7	52.5	[illegible].5
Carcinoma	14	9 7	64 1	14.0
Total	145	100.0	60.5	10.5
Control group				
Atrophic endometrium	48	87.3	63.0	13.[illegible]
Slightly proliferative endometrium	6	10.9	60.8	12.7
Endometrial polyp + atrophic endometrium	1	1 8	57.5	13 0
Total	55	100.0	62.8	13.2

tion of the bleeding time coagulation time, fibrinogen value, prothrombin index (thrombotest Owren), serum calcium and thrombocyte count. No pathological results were obtained.

Patients with cervical carcinoma were omitted from the series.

METHODS

The urinary excretion of oestrone, oestradiol and oestriol was determined during three consecutive days by the method of Adlercreutz et al. (1967) and Adlercreutz & Luukkainen (1968).

Vaginal smears were studied by the method of *Papanicolaou* and *Traut* (1943). The oestrogenic effect was determined by calculating the karyopyknotic index (KI) and eosinophilic index (EI), which represent the mean percentages of karyopyknotic and eosinophilic cells. Eosinophilic cells with a nuclear diameter of at least 6 μ were regarded as karyopyknotic cells. Cells corresponding in shape and size to superficial cells and with a plasma readily stained by eosin were counted as eosinophils. A pyknotic nucleus was not considered a necessary criterion. These two indices together illustrate very well the oestrogen activity in vaginal smear (Pundel, 1958 Wachtel, 1958 and 1960). In some of the present cases genital prolapse or vaginitis prevented the determination of KI and EI.

When all vaginal smears and urinary samples required for oestrogen determination had been obtained, curettage was performed in order to obtain an endometrial biopsy specimen for histological investigation.

RESULTS

The histological structure of the endometrium, the number of cases, the mean age and the mean time lapse after the menopause are shown in Table I. Atrophic endometrium was observed in 22.8 % of the patients in the bleeding group. In all of these cases bleeding was very scanty. Another 6 patients had atrophic endometrium + an endometrial polyp, and 7 patients had atrophic endometrium + a cervical polyp. Most of these patients were elderly and the interval between the menopause and the onset of bleeding was longer in these cases than in the remainder. Those patients who exhibited an oestrogen effect in the endometrium varying in degree were younger the interval between the menopause and the onset of bleeding was shorter and bleeding was more profuse. An endometrial polyp was present in 9 cases. Secretory endometrium was observed in one patient she was 52.5 years old and the time lapse since the last menstruation was [illegible].5 years. Fourteen patients, mostly of the older age groups, had endometrial carcinoma. The control group consisted almost exclusively of patients with atrophic endometrium. The mean age was slightly higher in this group than in

tions did not differ from the values for the controls, which throughout were low.

In some patients with an endometrial polyp an oestrogenic effect varying in degree was observed in the endometrium, and the development of the polyp can be explained on this basis. In other cases, however, the endometrium was atrophic. In these, the polyp may be considered a result of local cellular changes.

The patients with endometrial carcinoma had a low urinary oestrogen excretion and a poor oestrogenic effect in the vaginal smear. This is in good agreement with previous results (Rauramo & Grönroos, 1963; Timonen & Tervilä, 1963; Charles et al. 1965; Procopé, 1968).

In elderly women signs of an increased oestrogen production may signify a pathological process, most often localized to the ovaries, but the possibility of the production of oestrogens from the adrenal glands should also be taken into account (cf. Procopé, 1968).

REFERENCES

Adlercreutz, H., Salokangas, A. & Luukkainen, T. Proceedings of symposium held at the University of Glasgow on 4 to 6 april 1966 (ed. J. K. Grant). University Press, Cambridge, 1967.

Adlercreutz, H. & Luukkainen, T. Proceedings of the Round Table on Gas Chromatography of Hormonal Steroids, applied to biological fluids, held May 23–25 1967 (ed. R. Scholler & M. F. Jayle). Gordon & Breach, New York, 1968.

Breuer, H., Nocke, W., Gessler, G. & Mitchell, F. L. Klin Wschr 35 672, 1957.

Brown, J. B. Memories of the Society of Endocrinology 3 1, 1955.

Brown, J. B. Endocrine aspects of breast cancer (ed. A. R. Currie), 197 pp. Livingstone, Edinburgh and London, 1958.

Brown, J. B. & Matthew, G. D. Recent Progr Hormone Res. *18* 337, 196_.

Charles, D., Bell, E. T., Loraine, J. A. & Harkness, R. A. Amer J Obstet Gynec 91 1050, 1965.

Davies, V. & Williams, G. F. J Obstet Gynaec Brit Emp 60 715, 1953.

Fahlund, G. T. & Broders, A. C. Amer J Obstet Gynec 51 22, 1946.

Frampton, J. J Obstet Gynaec Brit Comm 73 137, 1966.

Furuhjelm, M. Acta Obstet Gynec Scand 45 352, 1966.

Grönroos, M. Acta Obst et Gynec Scand 43 Suppl. 3, 1965.

Kottmeier, H.-L. Acta Obstet Gynec Scand 27 Suppl. 6, 1947.

Lajos, L., Fiel, G., Kecskés, L., Görcs, J., Mutschler, F. & Kobór, L. J Obstet Gynaec Brit Comm 70, 1016, 1963.

Lehto, L. & Kiesmäki, O.: Gynaecologia (Basel) *143* 391, 1957.

Lyngbye, J. & Mogensen, E. F. Acta Endocr (Kbh.) 36, 350, 1961.

McBride, J. M. J Clin Endocr *17* 1440, 1957.

Nissen-Meyer, R. & Sanner, T. Acta Endocr (Kbh.) *44* 325, 1963.

Noer, T. Acta Path Microbiol Scand *51* 193, 1961.

Novak, E. J Clin Endocr 4 575, 1944.

Novak, E. & Richardson, E. H., Jr. Amer J Obstet Gynec 42, 564, 1941.

Novak, E. R., Goldberg, B., Jones, G. S. & O'Toole, R. V. Amer J Obstet Gynec 93 669, 1965.

Papanicolaou, O. M. & Traut, H. F. Diagnosis of uterine cancer by the vaginal smear. The Commonwealth Fund, New York, 1943.

Parks, R. D., Scheerer, P. P. & Greene, R. R.: Surg Gynec Obstet *106*, 413, 1958.

Procopé, B.-J. Acta Endocr (Kbh.) 60: Suppl. 135, 1968.

Pundel, J. P. Acta Cytol (Philad.) 2 347, 1958.

Rauramo, L. & Grönroos, M. Ann Chir Gynaec Fenn *52* 351, 1963.

Timonen, S. & Tervilä, L. Ann Chir Gynaec Fenn *52* 147, 1963.

Wachtel, E. Acta Cytol (Philad.) 2, 633, 1958.

— Acta Cytol (Philad.) 4 65, 1960.

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Table III. *Histological structure of the endometrium, no of cases, urinary excretion of oestrogens and mean value of KI and EI in vaginal smear in the control group*

M = median value. Oestrogen values and mean KI and EI values in brackets indicate range

Histological structure of the endometrium	No. of cases	Urinary excretion of oestrogens (µg/24 hr) Oestrone	Oestradiol	Oestriol	Total oestrogens	KI and EI in vaginal smear (mean value)
Atrophic endometrium	48	M 1.1 (0.4–4.6)	M 0.9 (0.0–[illegible].6)	M 5.3 (1.9–19.0)	M 7.8 (2.5–21.7)	M 8.2 (0–15)
Slightly proliferative endometrium	6	M 1.5 (0.6–3.0)	M 0.8 (0.0–1.5)	M 7.1 (4.8–8.0)	M 8.8 (6.3–12.0)	M 15.5 (0–25)
Endometrial polyp + atrophic endometrium	1	4.1	0.1	8.5	12.7	0
Total	55	M 1.4 (0.4–4.6)	M 0.85 (0.0–2.6)	M 5.7 (1.9–19.0)	M 8.0 (2.5–21.7)	M 8.6 (0–25)

oestrogenic effect in the vaginal smear in these groups did not differ from the corresponding values in the control group which throughout were low On the other hand, those patients in the bleeding group who showed a stronger oestrogenic effect in the endometrium and in the vaginal smear had a clearly increased excretion of urinary oestrone oestradiol and oestriol, although some overlapping occurred. Of the various urinary oestrogen values (oestrone, oestradiol, oestriol and total oestrogens) the total excretion showed the most obvious correlation with an oestrogenic effect in the endometrium although overlapping occurred. Moreover clearly elevated urinary oestrogen values and an increased oestrogenic effect in the vaginal smear as compared with the control group, were noted in the bleeding patients showing an endometrial polyp The patients with a cervical polyp had slightly elevated values

DISCUSSION

In cases of post-menopausal uterine bleeding the cause of the bleeding must always be ascertained by curettage If an oestrogenic effect is observed in the endometrium, it is advisable also to determine the urinary oestrogen excretion and the oestrogenic effect in a vaginal smear The urinary oestrogen excretion reflects the oestrogen production of the organism at the time of the study while an oestrogenic effect in a vaginal smear is an expression of more persistent oestrogen production, and an oestrogenic effect in the endometrium is indicative of oestrogen production for an even longer period of time.

In addition, the conversion of an inactive steroid to a biologically active compound at the end organ and the possibility of a differential response of target organs deserve consideration and might explain such an unexpected finding as that of a hyperplastic endometrium in conjunction with an atrophic vaginal smear (Novak et al., 1965)

Moreover it should be taken into account that only part of the oestrogenic components are measured by chemical determination of urinary oestrogens.

Considering these facts it is understandable that the urinary oestrogen excretion, an oestrogenic effect in the vaginal smear and the histological structure of the endometrium are not always correlated.

A positive correlation was observed between the urinary oestrogen excretion, an oestrogenic effect in vaginal smears and an oestrogenic effect in the endometrium, although overlapping occurred In those cases in the bleeding group in which an oestrogenic effect in the endometrium varying in degree was noted, the time lapse since the menopause was shorter than in the remainder of cases. The urinary excretion of total oestrogens and the mean KI and EI in vaginal smears were higher than the corresponding values for the control group to a degree that was statistically significant. However the values noted for those patients in the bleeding group who showed atrophic or only slightly proliferative endomet

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ORAL CONTRACEPTIVES AND GLUCOSE TOLERANCE

A Clinical Study of Three Different Oestrogen-Progestogen Combination

Sigvard L. Pehrson

From the Department of Obstetrics and Gynaecology (Head: Prof. Sam Brody), University of Göteborg, Göteborg, Sweden

Abstract Three oral contraceptives with different oestrogen-progestogen combinations were given to 22 women of fertile age. The possible diabetogenic effect was studied after intravenous glucose tolerance test before the treatment was started and after 1, 6 and 12 months of cyclical therapy. All of the women had a normal menstrual cycle before treatment began. They showed none of the features which suggest prediabetes. The *k* and the T½ values were calculated. The intra-individual variation of *k* between two tolerance tests was calculated on the basis of figures available in the literature. When the *k*-value did not rise linearly, attempts were made to calculate the variation within different *k*-value ranges. The possible diabetogenic effect of the three different drugs was studied in the light of these calculations. In the cases tested, Drug no. 1, which contained nor-ethisterone acetate (4 mg) + ethinyl-oestradiol (0.05 mg) (Anovlar), and Drug no. 2, which contained megestrol acetate (4 mg) + ethinyloestradiol (0.05 mg) (Volidan) did not seem to have any diabetogenic effect. On the other hand, Drug no. 3, which contained ethynodiol acetate (1 mg) + mestranol (0.1 mg) (Ovulen), appears to have had a transient diabetogenic effect. It was slightly evident after one month of treatment, statistically significant after 6 months and practically negligible after 1 year of treatment. Further experiments with specific hormones are indicated. Women in the danger zone, i.e. women who have latent diabetes or are in a prediabetic stage should be included in these investigations.

That pregnancy has a diabetogenic effect has been reported by a number of investigators (Burt, 1956, 1960; Bergqvist, 1954; Horvitz, 1937; Hoet, 1954; Pyke, 1956; Kyle, 1963; O'Sullivan, 1966 and others). Women with subclinical diabetes can develop a manifest form of the disease. If they were in the prediabetic, undiagnosable stage before pregnancy, a glucose tolerance test during pregnancy can reveal subclinical or even manifest diabetes.

It is conceivable that the state of pseudo-pregnancy evoked by oral contraceptives is responsible for a similar modification of glucose metabolism in a diabetic direction. There exist both theoretical and experimental grounds for this.

Ingle (1943) showed that oestrogen had a diabetogenic effect in rats. Corticosteroids caused a change in glucose metabolism similar to that found in diabetes mellitus in man (Sprague, 1950; Conard, 1955; Holten, 1957; Grodsky, 1960). Treatment with anabolic steroids resulted in a lowering of the *k* value after an intravenous glucose tolerance test (Landon, Wynn, 1962, 1963). Oestrogens potentiated the diabetogenic action of corticosteroids (Nelson, 1963). Oestrogens and 19-nor-steroids produced an increase of the plasma cortisol concentration (Layne, 1965).

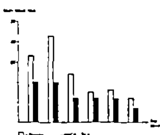
Great interest has been shown in the secondary effects of contraceptives. Wynne (1963) reported elevated blood sugar values in women treated with these drugs, and Gersberg (1964) was able to demonstrate that they had a distinct diabetogenic effect. An increased content of plasma corticosteroids was reported by Metcalf (1963) and others. Since then several reports have been published on the diabetogenic effect (Spellacy, 1965, 1966, 1967; Peterson, 1966; Buchler, 1966; Wynn, 1966; Posner, 1967; Puchulu, 1967; Danowski, 1968; Pyörälä, 1968; di Paola, 1968). Oral glucose loading has been the main method used in the experiments (Gersberg, Buchler, Wynn) but intravenous glucose tolerance test has also been employed (Buchler, Posner, Spellacy, Wynn, di Paola). Investigations of the plasma insulin content have also been made (Spellacy, 1966, 1968). Some of the reports, however, have discounted the diabetogenic effect (Butterman, 1967; Frerichs, 1967; Lunell, 1967; Starup, 1968).

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Hematuria and so-called essential hematuria: 2–3 tablets (1–1.5 g) –3 times daily until macroscopic hematuria is no longer present.
Menorrhagia: 2 tablets (1 g) 3–6 times daily as required, for 3–6 days. Treatment should start only when bleeding has become profuse.

Nilsson, L., Rybo G. Treatment of menorrhagia with an antifibrinolytic agent, tranexamic acid (AMCA). A double blind investigation. Acta Obstet. Gynecol. Scand. 46 (1967) p. 57

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It is conceivable that the state of pseudo-pregnancy evoked by oral contraceptives is responsible for a similar modification of glucose metabolism in a diabetic direction. There exist both theoretical and experimental grounds for this.

Ingle (1943) showed that oestrogen had a diabetogenic effect in rats. Corticosteroids caused a change in glucose metabolism similar to that found in diabetes mellitus in man (Sprague, 1950; Conard, 1955; Holten, 1957; Grodsky 1960). Treatment with anabolic steroids resulted in a lowering of the *k* value after an intravenous glucose tolerance test (Landon, Wynn, 1962, 1963). Oestrogens potentiated the diabetogenic action of corticosteroids (Nelson, 1963). Oestrogens and 19-nor-steroids produced an increase of the plasma cortisol concentration (Layne, 1965).

Great interest has been shown in the secondary effects of contraceptives. Wayne (1963) reported elevated blood sugar values in women treated with these drugs, and Gersberg (1964) was able to demonstrate that they had a distinct diabetogenic effect. An increased content of plasma corticosteroids was reported by Metcalf (1963) and others. Since then several reports have been published on the diabetogenic effect (Spellacy, 1965, 1966, 1967; Peterson, 1966; Buchler, 1966; Wynn, 1966; Posner, 1967; Puchulu, 1967; Danowski, 1968; Pyörälä, 1968; di Paola, 1968). Oral glucose loading has been the main method used in the experiments (Gersberg, Buchler, Wynn), but intravenous glucose tolerance test has also been employed (Buchler, Posner, Spellacy, Wynn, di Paola). Investigations of the plasma insulin content have also been made (Spellacy 1966, 1968). Some of the reports, however, have discounted the diabetogenic effect (Butterman, 1967; Frerichs, 1967; Lunell, 1967; Starup, 1968).

Table I *Number of patients treated with 3 different progestogen–oestrogen combinations*

Drug no. 1 = Anovlar no. = Volidan, no 3 = Ovulen

No. of patients	Progestogen	Oestrogen	Drug no
6 (7)	Norethisterone acetate 4 mg	Ethinyloestradiol 0.05 mg	1
6	Megestrol acetate 4 mg	Ethinyloestradiol 0 05 mg	2
8 (9)	Ethynodiol acetate 1 mg	Mestranol 0 1 mg	3

In this work, the effect of three different oestrogen-progestogen combinations on glucose tolerance has been studied. An intravenous glucose tolerance test was carried out prior to commencing treatment and after 1 6 and 12 months of cyclical treatment.

MATERIAL AND METHOD

Three different commercially available contraceptives were given to 22 women of fertile age (see Table I). The obstetrical history was taken and the presence of a family history of diabetes was recorded. Si of the women had not given birth t children. The others had 1–4 children. No women with a family history of diabetes or with other features leading to any suspicion of prediabetes were included in the series. None of their children had a birth-weight of 4.5 kg or more At the start of the treatment all of the women were subjectively healthy and had normal menstrual cycles. None of them were abnormally obese Their mean age was 3 years.

After a 1 -hour fast, 25 g of glucose as a 50% solution were administered intravenously The subjects had an adequate carbohydrate intake during the days preceding the injection. The investigation was conducted during the first week of a cycle and during the first cycle week of the month prior to the beginning of the treatment. All the women were ambulatory and sat up during the tests. No significant general or local reactions could be noted after the glucose injections.

Table II *K-values before and after 1 6 and 12 months of treatment with norethisterone acetate 4 mg and ethinyloestradiol 0.05 mg (Drug 1)*

Case no	P rity	Age	K value: Before	1 month	6 months	1 months
		41	2.04	2.31	67	3 47
9	1	27	2.31	2.89	2.67	89
31	3	35	10	3 30	2.89	2.77
1	4	40	4	2.31	2.17	48
3		33	1 69	4	1 78	1 69
18	0	25	4 08	3 47	3 85	4 6
1	0	26	(1 95)	—	—	—
Mean			2.41	2.75	2.64	2.98

Twenty of the women were given a repeated glucose tolerance test after 1 month of treatment. In 19 cases another injection was given after 6 months of cyclical treatment, and in 9 cases 1 months after the initial injection. There was no change of drug during the series of tests. A blood sugar test was made before the glucose injection and 10, 20, 30 40 50 and 60 min after the end of it. The blood sugar was determined ith glucose oxidase reagent (Kabi AB, Stockholm, S eden) and the k value using Hamilton & Stein s method (1942). th the absolute glucose alues in milligram per cent was calculated. The half-time ($T\frac{1}{2}$) of the glucose concentration was also calculated.

$$k = \frac{69.3}{T\frac{1}{2}}$$

For the calculation of k and $T\frac{1}{2}$ the graphic method of Amatuzio (1953) was employed.

RESULTS

Seven women took oral contraceptives containing norethisterone acetate (4 mg) – ethinyloestradiol (0 05 mg) (Anovlar) (Drug no 1) The age distribution and number of deliveries are given in Tabl II. The mean k value of this group was 2.41 before

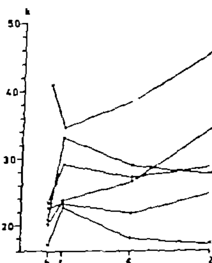


Fig 1 K alues bef re nd after 1 6 and 1 months of tre tment with norethisterone acetate 4 mg and ethinyloestradiol 0 05 mg (Drug 1)

reatment. One woman did not return for further glucose tolerance test after 1 month, and is not included in the series. After 1 month of treatment the mean *k*-value rose to 2.75. A study of the individual observations shows that the *k*-value rose in 6 women. In 1 case a slight decline in value could be noted. The woman who showed this slight reduction had from the outset a remarkably high initial value. The *k* value sank by 0.61. A $T_{\frac{1}{2}}$ calculation gave an average of 31 sec before treatment and 26 sec after a month.

After 6 months of treatment the mean *k*-value was 2.46, i.e. slightly higher than the initial value but somewhat lower than after 1 month of medication. This difference, however, is negligible, and even in the individual cases no more marked change was recorded.

After 1 year of treatment with Drug no. 1 the mean *k* value had increased somewhat, or to 2.98. However, this rise is insignificant. The $T_{\frac{1}{2}}$ had increased by 5 sec. The patient who had slightly lower *k* value after a month of treatment showed after 1 year an increase to a value above the initial one. The changes in *k* value are shown graphically in F g. 1.

Six women were treated with drug containing megestrol acetate (4 mg) – ethinyloestradiol (0.05 mg) (Volidan) (Drug no. 2). In 1 case no results could be drawn from the first intravenous glucose injection because wrong reagent was used. The mean *k*-value for the remaining 5 cases was 2.37 (Table III). After 1 month of treatment it had decreased to 2.19. All 6 women are included in this figure. The individual variations in this group were somewhat larger than in the former group.

Table III. K-values before and after 1, 6 and 12 months of treatment with megestrol acetate 4 mg–ethinyloestradiol 0.05 mg (Drug 2)

Case no.	Parity	Age	K-value: Before	K-value: 1 month	K-value: 6 months	K-value: 12 months
1	2	34	3.47	2.17	2.67	—
6	2		2.24	3.15	1.73	—
7	3	36	—	1.47	2.24	—
8		35	2.94	1.26	—	—
10	1	22	3.67	2.09	2.37	—
21	2	37	1.44	2.31	1.69	—
Mean			2.37	2.19	2.18	



Fig. 2. K-values before and after 1, 6 and 12 months of treatment with megestrol acetate 4 mg—ethinyloestradiol 0.05 mg (Drug 2).

Three women showed a slight rise in *k*-value. Two showed a moderate reduction. The mean $T_{\frac{1}{2}}$ value was 30 sec prior to the first treatment and 35 sec after 1 month of treatment.

Another glucose tolerance test after 6 months of treatment gave a mean *k*-value of 2.18 for the remaining 5 patients, i.e. the same value as after 1 month of treatment. The individual variation was now relatively large. The individual observations are given in *Table II*, and graphically in *Fig. –*. Since Drug no. 2 was no longer available after 6 months of treatment, this series was discontinued. Other drugs were used in subsequent treatment.

The third group started with 9 women. They were treated with a drug containing ethynodiol acetate (1 mg) – mestranol (0.1 mg) (Ovulen) (Drug no. 3). The mean *k*-value when the glucose was injected intravenously before starting treatment was 2.40. After 1 month of medication 1 woman left the trial. The mean *k* value for these 8 women fell from –.56 to 2.22. In 5 cases the *k* value sank by between 1.47 and 0.32 (see Table IV). In 3 cases a slight rise was observed. That the reduction in 2 cases was as large as 1.47 and 1.45 respectively is worthy of note. The $T_{\frac{1}{2}}$ values had a mean of 27 sec before treatment and 31 sec after a month. In the 2 cases which showed the largest decrease in *k*-value, the $T_{\frac{1}{2}}$ value was also considerably extended. It increased by 16 and 24 sec. In the other 3 cases where the *k* value declined, the $T_{\frac{1}{2}}$ extension was insignificant, 4.2 and 1 sec. Three cases of a rise in *k*-value and a shorter $T_{\frac{1}{2}}$ were also observed.

After 6 months of treatment the mean *k*-value

Table IV *K values before and after 1 6 and 12 months of treatment with ethynodiol acetate 1 mg and mestranol 0 1 mg* (*Drug 3*)

Case no	Parity	Age	*K*-value Before	1 month	6 months	12 months
3	3	40	3 80	3 47	2.57	—
4	2	33	1.58	2.48	1 14	—
5	0	29	3 47	1 98	1.87	—
13	3	38	3 15	2.67	1 69	2.31
14	2	33	1.24	1 73	1.51	—
15	0	23	2.10	2.17	1.58	2.57
16	0	24	(1 12)	—	—	—
22	2	26	2.89	1 44	2.17	2.17
24	0	22	2.24	1 78	1 61	1.98
Mean			2.40	2.22	1 77	2.26

continued to decline. It fell from an initial value of 2.56 to 1 77 Relative to the second test, the *k* value declined in 7 of the 8 cases studied. Relative to the *k* value before treatment, a decreased value was also noted in 7 of the 8 women.

In 4 cases additional glucose was injected after 12 months of continuous treatment. Three of the women who previously had showed a distinct decline in *k* value now showed a rise towards their pre-treatment value. The mean *k* value became 2.26 The $T\frac{1}{2}$ calculations for this drug showed an average rise of 4 sec after 1 month of treatment and of 12 sec after 6 months. A check made after 1 year indicated that the mean value had risen to 31 sec (see Fig 3)

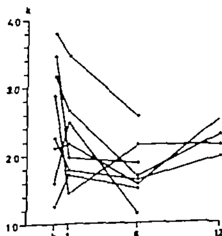


Fig 3 K alues befor and after 1 6 and 1 months of treatment with ethynodiol acetat 1 mg nd mestranol 0.1 mg (Drug 3)

DISCUSSION

In earlier work, the glucose tolerance tests w frequently not given until after several months treatment and true control material was often la ing In one and the same test series, the gluc tolerance tests were done after treatment peri of varying length. Sometimes the results were bas on the summary of experience obtained with d ferent drugs. In most of the investigations t treatment was cyclical although continuous tre ment was also used. In some cases sequential dru were employed.

To carry out an investigation of this kind it essential to establish standardized experiment conditions and a precise test method with hi reproducibility The oral glucose method is le suitable in this context. It has a large individu variation (West, 1964 McDonald, 1965 O'Su livan, 1966)

The intravenous method is regarded as superi partly because of its high reproducibility and par ly because of its negligible effect on the release c insulin from the pancreas during the tests. I would be advisable to study the basal glucos metabolism (Franckson, 1962 Hales, 1963 E rick, 1964) But there are still a number of prob lems associated with the intravenous method. Th *k* value obtained when determining the assimila tion rate does not increase linearly With lo *k* values, such as 1–1.20 an increase of $T\frac{1}{2}$ b 1 sec, for instance, produces an increase of *k* by only 0 01–0 02, whereas an equivalent extensio of the time with high *k* values, such as 3 00–3.20 increases the *k* value by 0 15–0.20 A minor ex tension of the half-life i.e. a displacement of the glucose metabolism towards a diabetic pattern will—if the person starts with a high *k* value— produce a dramatic decline of *k* while a cor responding time change in a person with a low *k* value from the start might be imperceptible. By using the half-time ($T\frac{1}{2}$) it is possible in part to get away from this. The relation between *k* and $T\frac{1}{2}$ is shown in Formula 1

Table V *Estimated k-value-difference in different k value-ranges*

K alue range	Difference between *K* and *K*
0.50–1 49	About 0.2
1.50–.49	About 0.5
2.50–3 49	About 1 4

The individual variations between two intravenous glucose tolerance tests have been studied by many authors. The mean value and the S.D of all the *k*-values have been calculated. No calculation has been made of the average *k*-value in different *k*-value classes. If the figures for the double loadings published in the literature are used (Conard, 1955 Duncan, 1956 Lunell, 1966) in an attempt to strike a mean and determine the dispersion in the *k*-value class 0.50–1.50, where the majority of the published cases are found, a mean variation of 0.90 ± 0.05 is obtained. This variation is equivalent in this *k* value range to a difference of 5 sec in the half-time ($T_{\frac{1}{2}}$) By adding 2 S.D a time difference of 10 sec would be obtained as the highest permissible difference. If a time difference calculated in this way is inserted in Formula 1 the highest permissible difference in *k*-value within the different *k*-value ranges can be determined (see Table V).

If this statistical method of calculation is applied to the material in this work, it is found that Drug no 1 and 2 did *not appear to have any* diabetogenic effect in the cases studied.

After month of treatment the use of Drug no. 3 gave an insignificant decline in glucose tolerance. This became more conspicuous after 6 months and must be regarded as statistically significant here. The mean *k*-value for this drug fell from 56 to 1 77 This decline is equivalent to a 12-sec extension of the half-time. After a year of treatment the mean *k*-value rose again to nearly its pre-treatment level. Thus, during this period the glucose tolerance had become normal.

The results of this work partially support earlier investigations which report a lowered glucose tolerance after an intake of oral contraceptives (Spellacy Peterson, Bochler and others). All these authors tested different drugs from those used in this work. Posner (1967) used ethynodiol acetate—mestranol, i.e. the same combination studied here Wynn work (1966) included number of women who received this drug. Very few experiments have been done on the other two drugs investigated in this work. No diabetogenic effect could be observed, which suggests that this may be feature of pecific hormones. Nor should variations in individual sensitivity be ignored. The inability of some authors to establish a diabetogenic effect may be related to these factors.

It is advisable to carry out further tests of specific sex hormones under standardized experimental conditions. Particularly women with a suspected prediabetic condition or with a known slightly lowered glucose tolerance should be made the subject of special study

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REFERENCES

Anasturio, D S Statemen, F L. & Vanderbilt, M. J J Clin Invest 32. 428, 1953.
Bergqvist, N. Acta Endocrin (Kbh) 15 166, 1954.
Bochler, D & Warren, J C. Am J Obst Gynec 95 479 1966.
Burt, R. L. Obstet Gynec 7 658, 1956.
— Clin Obst & Gynec 3 310, 1960
Buttermann, P Munchen Med Wschr 13 645, 1967
Conard, V Acta Gastro-Enterolog Belg 18 654, 1955
Dasowski, T S, Sabeh, G Alley R. A., Robbins, T. J Tsai, C. T & Sekaran, K. Clin Pharmacol Therap 9 223, 1968.
Duncan, L. J P Quart J Exp Physiol 41 85 1956.
Ehrlich, L., Stummler L., Hand, C. J & Aral, Y J Clin Endocrin 24 1076, 1964
Franckson, J R. M Ooms, H. A., Bellens, R., Conard, V & Bastenie, P A. Metabolism 11 482, 1962.
Frerichs, H Gross, S Severidt, E. & Creutzfeldt, W 12 Symp. Deutsch. Ges. Endokrinologie. Wiesbaden, 1967
Gershberg, H., Javier, Z. & Hulse M Diabetes 13 378, 1964
Grodsky G. M. & Forsham, P H. J Clin Invest 39 1070, 1960.
Grodsky G. M., Karam, J H., Pavlatos, F & Forsham, P H. Metabolism 12 278, 1963
Hagbard, L., Acta Obstet Gynec Scand 37 497 1958.
Hales, C. N & Randle P J Biochem J 88 137 1963.
Hamilton, R. & Stein, A. F J Lab Clin Med 27 491, 1942.
Hort, J & Lukens, F D W Diabetes 3 1, 1954.
Holten, C., Lundbaek, K. & Staffeldt, L. Acta Med Scand 157 275 1957
Horwitz, F & Irving, F Am J M Sci 194 85 1937
Ingle, D J Am J Physiol 138 577 1943.
Kyle, G C Ann Intern Med 59 Suppl. 3, 1 1963
Landon, J Fawcett, J. K. & Wynn, V J Clin Path 15 579, 1962.
Layne, D. S. & Meyer, C J Metabolism 14 429 1965.
Lunell, N.-O Acta Obstet Gynec Scand 45 Suppl. 4, 1966.
— Symp Peroral Antikonception (ed. C. Gemzell). Uppsala, 1967

McDonald, G W Fiscer G F & Burnham, C. Diabetes *14* 473 1965
Metcalf, M. G. J Endocr *26* 15 1963
Nelson, D H, Tanney H, Mestman, G Gieschen, V W & Wilson, L D J Clin Endocr Metab *23* 61 1963
di Paola, G, Puchulu, F Robin, M, Nicholson, R & Marti, M Am J Obst Gynec *101* 206, 1968
Peterson, W F Steel, M & Coyne, R V Am J Obst Gynec *95* 484 1966.
Posner N A, Silverstone F A, Pomerance, W & Baumgold, D. Obstet Gynec 29 79 1967
Posner N A, Silverstone F A, Pomerance W & Singer N. Obstet Gynec *29* 87 1967
Puchulu, F Jr di Paola, G M, Nicholson, R M & Groppa, S. 6th Congr Int. Diab. Fed. Excerp. Med. no. 140, 1967
Pyke D A. Lancet *1* 818 1956.
Pyörälä, K, Pyörälä, T & Lampinen, V Lancet 776, 1968
Spellacy W N & Shoeller K L. Clin Res *13* 407 1965
Spellacy W N & Carlson, B. S. Am J Obst Gynec *95* 474 1966.
Spellacy W N, Carlsson, K L & Buhi, S. A. Diabetes *16*. 590 1967
Spellacy W N Carlson, K L & Schade, R N. Am J Obst Gynec *101* 672, 1968
Sprague, R. G., Power M H, Mason, H. L, Mathieson, D R, Hench, P S, Kendall, E. C, Slocumb, C. H. & Polley H. F Arch Intern Med *85* 199 1950
Starup, J Date, J & Deckert, T Acta Endocr 58 537 1968
O'Sullivan, J B. & Mahan, C. M Diabetes *13* 278 1964
— Am J Clin Nutrit *19* 345 1966.
Wayne H, Frieden, E. H, Caplan, H. L & Cole, T Arth & Rheumat *6* 796, 1963
West, K, Wulf, J Riegel, D & Fitzgerald, D Arch Intern Med *113* 641 1964
Wynn, V & Doar J W H. Lancet 2 715 1966.

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POST-OPERATIVE WOUND COMPLICATIONS

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Abstract. The wound complications occurring after a total of over 32 000 gynaecological operations from 1955 to 1967 have been analysed. The average rate of infection was 2.9%. Staphylococcus aureus was found in 29% of cases and in 24% of swabs E. coli was observed. Altogether Gram-negative bacilli were found in 27% of the infected wounds. Clear differences can be noticed in the numbers of complications following different operations, the fewest complications occurring after abortion made by hysterotomy and operations for malignant disease, and the greatest number after total hysterectomies and operations for incontinence. Prophylactic appendicectomies increased the rate of wound infections to 4.3%.

The protection of operative wounds from infection and other complications is achieved primarily by maintaining strict asepsis in surgical hospitals. Absolute asepsis, however, can never quite be attained. There seems little room for doubt that even in the best organized operating theatres and wards, and even with the protection of antibiotics, postoperative wound infections will cause complications in some of the patients.

The present analysis of a fairly large series was designed to throw light on the problem by determining the incidence of wound complications by age and by type of operation in two Departments of Gynaecology. The data on surgical cases have been compared annually from 1955 to 1967, attention being paid to the bacteriological grading and to the incidence of wound infection.

MATERIALS AND METHODS

The present series comprises 32 421 surgical cases treated in the First and Second Departments of Gynaecology, University Central Hospital, Helsinki, Finland, during 12 years, from 1955 to 1967. Altogether 934 patients had post-operative wound complications in this gynaecological series. Accordingly the total incidence of wound complications was 2.9%. One per cent of the patients with wound complication stayed in the hospital less than 10 days, 59% of them over 10 but under 20 days, and the remaining 40% over 20 days.

The wound complications considered in this paper were diagnosed in hospital. The material has been divided into two groups, according to whether infection was primary or followed the development of a haematoma.

RESULTS

Bacteriological examination of wounds

A bacteriological swab was taken from the wounds of 279 patients, i.e. in a third of the cases with a complication. Table I shows that Staphylococcus albus or a negative swab was found in 27% of cases, and pyogenic Staphylococcus in 29% of cases. In 24% of swabs E. coli was observed. The rates of Proteus and Pseudomonas were very low: 2.5% for the former and 0.7% for the latter. Altogether Gram-negative bacilli were found in 27% of the infected wounds.

Annual incidence of wound complications

The incidence of wound complications is presented in Fig. 1. It is seen that the total number varied from 50 to 80 per year during the period 1955 to 1967 excluding the two "infection" years, 1960 and 1964. In both these years there were about 130 surgical wound infections per year which is about twice the average rate during the entire period of observation. The most interesting feature of Fig. 1, however, is the last 3 years, from 1965 to 1967. During this period there were only about 30 cases annually, which is about half the previous level.

The annual distribution of operations and wound complications

Table II shows the annual frequency of wound complications in operations of different types. It

Table I *Bacteriological grading of swabs from infected wounds*

Year	Number of swabs	Negative or Staph. albus	Only sensitivity taken	Staph. aureus	Phage-typed Staph. aureus	E. coli	Proteus	Pseudomonas	Other pathogenic bacteria
1955	3	—	2	—	—	—	—	—	—
1956	5	—	5	—	—	—	—	—	—
1957	11	—	8	—	—		—	—	
1958	9	—	9	—	—	—	—	—	—
1959	18	—	4	13	7		—	—	—
1960	50	10	—	4	1	11	—	—	8
1961	-7	4	—	8	3	1		—	7
196-	31	10	—	16	4	6	1	1	—
1963	18	3	—	5	1	10	1	—	1
1964	63	31	—	9	-	13	1	1	9
1965	13	6	—	2	1	4	—	—	
1966	14	7	—	2	1	3	1	—	1
1967	17	3	—	3	—	3	1	—	8
Total	79	74	28	82	31	66	7		39
Per cent	100	-7	10	29	11	24	-5	0 7	14

can be seen that the numb-r of operations per year did not change essentially during the 13 years, especially the years from 1956 to 1967 are comparable. Both the number and percentage of wound complications are shown in Table II and Fig 2 for a few of the commonest types of operations. It can be seen that there have been no specific changes in the incidence of wound complications in any particular type of operation, but that the changes follow the average trend of wound infections Clear differences can be noticed in the numbers of complications following different operations, the fewest complications occurring after abortion made by hysterotomy and operations for malignant disease, and the greatest number after hysterectomy and operations for incontinence The frequency of haematomas was essentially constant but that of infected ones was variable, depending on the type of operation From the data in Table II a comparison can be made between the two ways of operating on the appendix, either by appendicectomy or by inversion of the appendix. There seems to be rather fewer complications following the technique of in-

Table II. *The numbers of operations and wound complications in various types operations from 1955 to 1967*

Year	Total number of operations	Total hysterectomies			Subtotal hysterectomies			Operations for malignant disease			Abortions made by hysterotomy		
		Oper	Comp.	%	Oper	Comp		Oper	Comp		Oper	Comp	%
1955	1 779	187	8	4.3	391	14	3 6	98	3	3 0	161	5	31
1956	2 034	244	11	4.5	470	1	4.5	117	6	5 1	20-	8	4[illegible]
1957	2 63	794	7	9.-	422	-6	6.-	118	3	2.6	-25		[illegible]
1958	2 592	316	16	5 1	401	14	3.5	160	7	4 4	-56	9	35
1959	876	410	4	5 6	331	13	3 9	141	6	4 3	301	10	33
1960	2 640	436	32	7.3	306	18	5 9	157	7	4 6	3 6	18	55
1961	508	380	28	7 4	-59	11	4	161	1	0 6	284	5	11
196-	2 466	372	4	6.5	274	1	4 4	15	8	5 3	308	1	3[illegible]
1963	2 421	435	18	4 1	177	12	6 8	184		1 1	335	11	33
1964	2 447	358	52	14.5	180	10	5 6	14	13	6 1	154	14	[illegible]
1965	794	564	8	1 4	178	3	1 7	215	1	0 6	-52	1	[illegible]
1966	490	596	7	1.2	148	1	0.7	-23	0	0	316	5	1[illegible]
1967	4	57	17	3 0	116	3	-6	43		0.8	330	2	[illegible]
Total	3 4 1	5 184	277	5.2	3 653	158	4.3	2 178	59	-7	1 650	102	-3

Oper = number of operations. Comp. = number of wound complications. % = percentage of wound complications

...ersion (Alfthan & Vara, 1966 Sjövall & Ursing, 1960), but the two groups are not fully comparable. In the first place, there were a few cases of appendicitis and in all of these appendicectomy was done and secondly the two groups are not comparable numerically There was no difference in the frequency of complications following the lower abdominal midline or the Pfannenstiel incision. On the other hand, the use of silk suture material in the skin was followed by significantly more frequent wound infections than the use of clips. In 73 cases prophylactic heparin was used after the operation. There seems to have been more haematomas in the group with heparin but the difference was not statistically significant. A similar result was obtained also by Zilliacus, Widholm & Vartiainen (1967).

DISCUSSION

The relative increase in the incidence of Gram-negative bacilli, especially Proteus and Pseudomonas, has come to be a major problem in most hospitals These bacteria are not common in the primary sources of infections, e.g. in the nares of staff The dust of wards and operating theatres seems to be the most important reservoir of several Gram-negative bacilli (Lowbury & Fox, 1954). *We feel that one of the most interesting* points that emerges from a consideration of the relatively low incidence of wound infections in our series is the probable importance of good

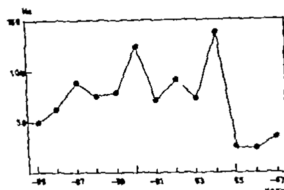


Fig 1 The annual numbers of wound complications.

cleaning staff and the high standard of hygiene maintained.

A few decades ago the organisms chiefly responsible for septic wounds were the B-haemolytic Streptococcus and Pneumococcus (Barber 1947 Finland, Jones & Barnes, 1959) To-day' problems are the penicillin-resistant Staphylococci and the Gram-negative bacilli. In 1960, the average incidence of post-operative wound infection was 9.7% (4.7 to 1.8) in 21 different surgical hospitals, according to the report of the Public Health Laboratory Service. Staphylococcus pyogenes was found in 60% of septic wounds and it was the *only pathogen found in 45% of cases. Coliform* bacilli were isolated together with Staph. pyogen. from 13% and alone from 17%

In our own series the average incidence of

...scopic pregnancies			Appendicectomies (prophylactic)			Inversions of appendix		
...per	Comp		Oper	Comp.	%	Oper	Comp.	%
123	1	6.5	458	5	1.1			
113	2	1.8	557	19	3.4			
128	2	1.6	771	40	5.2			
122	5	4.1	856	32	3.7			
112	1	0.9	894	35	3.9			
118	7	5.9	832	32	4.3	11	0	0.0
91	0	0	776	43	5.5	17	1	5.9
101	6	5.9	712	34	4.8	59	2	3.4
93	1	1.1	698	34	4.9	51	2	3.4
9[illegible]	6	6.5	744	57	7.7	48	5	1.0
72	2	2.8	646	18	2.8	72	0	0.0
64	1	1.2	610	7	1.1	181	3	1.7
89	1	1.1	596	13	2.2	162	3	1.9
1379	43	3.1	9150	389	4.3	601	16	2.7

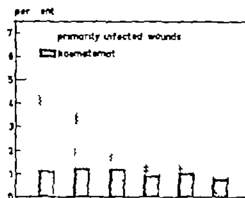


Fig Relative frequencies of wound complications after different types of operation. *1* Total hysterectomy *2* Sub-total hysterectomy *3* Ectopic pregnancy *4* Abortion made by hysterotomy *5* Incontinence *6* Malignancy

wound complications has been as low as 2 9% during the last 13 years. Usually much higher values have been reported in general surgical hospitals, e g. Campbell (1965) 17 % Clarke (1956–57) 13 6% in two general surgical departments, Gillespie, Alder Ayliffe, Bradbeer & Wypkema 1959) 36 1% in the male surgical wards and 1 6% in the operating theatres. Jeffrey & Sklaroff (1958) found serious infections in 9 8% and some infection in 26.1% of their cases. In the present series the incidence in 1960 and 1964 was also high, but on both occasions, it was brought under control. As long ago as 1955 Blowers, Mason Wallace & Walton showed how difficult the control of hospital infections can be They reported that the frequency of infections in a thoracic surgery unit was decreased from 10 9 to 3.9% by closing the operating theatres and wards, and by simultaneous thorough cleaning however it subsequently rose again to 6 2% Campbell (1965) showed that the prophylactic administration of penicillin reduced postoperative wound infections significantly In her series 77% of infections were caused by penicillin resistent Staphylococci. Similar observations were made by Rountree, Harrington Loewenthal & Gye (1960) and by Barber (1961)

The exceptionally low incidence of post-operative wound infections in the present series is explained by the compulsory inspection of hospital hygiene and cleaning and the repeated observation of nasopharyngeal carriers of pathogenic organisms. In several countries the fundamentally important work as far as hospital infections are concerned namely the cleaning of the hospital, is performed by a staff derived from countries with a lower standard of living and with less awareness of the importance of hygiene. This may be one reason for the fact that in this series infections with Pseudomonas, which thrives in dust reservoirs, amounted to only a few per cent. In several other large series much higher proportions of infections caused by this bacillus have been reported, up to 30 to 50

One of the most striking features was the very low incidence of wound infections in the operations for malignant disease, in which the condition of the patients must usually have been worse than average, and in which the operations themselves must have been more complicated than average The only conceivable explanation is that these operations were always performed by a senior surgeon, probably by a technique which demands more skill than usual The higher frequency of wound infections in the hysterectomy group is probably caused by opening the vagina. Similarly in the cases where the intestine was operated on or appendicectomy was performed the frequency of infection was higher too. A higher incidence of E. coli in the wounds after intestinal operations was also observed

REFERENCES

Allthan, O. & Vara, P Ann Chir Gynaec Fenn 55 C, 1966.

Barber M. J Path Bact 59 373 1947

— J Clin Path 14 , 1961

Blowers, R., Mason, G. A., Wallace K. R. & Walton, M. Lancet II 269 1955

Campbell, P Lancet II 806 1965

Clarke S Brit J Surg 44 592, 1956–1957

Finland, M Jones, W & Barnes, M J Am Med Ass 170, 188 1959

Gillespie, W Alder V Ayliff G Bradbeer J & Wypkema, W Lancet II 781 1959

Jeffrey J & Sklaroff, S Lancet I 365 1958

Lowbury E. & Fox, J J Hyg (Camb) 52 403 1954

Public Health Laboratory Service Lancet II 659 1960.

Rountree, P Harrington, M Loewenthal, J & Gye R. Lancet II 1 1960

Sjovall, A & Ursing, I Forhandlingar vid Nordisk Föreningen for Obstetrik och Gynekologi 11 Kongress 18–20 Augusti 1960 Helsingfors (p 89)

Zilliacus, H Widholm, O & Vartiainen, E Nord Med 77 540 1967

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CLEAR CELL ADENOCARCINOMA OF THE FEMALE GENITAL TRACT

A Report of Four Cases

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Abstract The incidence of clear cell type adenocarcinoma in the different parts of the genital canal, the age distribution of the patients, the clinical and histological picture and the theories advanced in the literature as to its histogenesis are reviewed. Four cases diagnosed in 1953–1968 at the Central Hospital of North Carelia are described. One of the tumours occurred in the vagina, two in the cervical canal and one in the ovary. The histopathological diagnosis may be difficult if pronounced secondary infection is associated with the tumour tissue and the tumour cells are well differentiated. Clear cell adenocarcinoma and Schiller mesonephroma are obviously two different histological manifestations of the same tumour and they may also occur combined in the same tumour. That the site of origin is in the remnants of the mesonephric duct must be regarded as still unproved.

Clear cell adenocarcinoma which is also known under other names such as mesometanephric rest tumour, mesonephric adenocarcinoma, mesonephroma and extra-embryonic mesoblastoma, is relatively uncommon tumour which is encountered chiefly in the ovaries and occasionally also in the cervical canal (McGee et al., 1962, Pomerance & Mackles, 1962 Tóth et al., 1964 Sharma et al 1967 Hameed, 1968, etc.) and in the vagina (Marlalek, 1942; Stroink, 1947 Plate, 1950 Novak et al., 1954 Tellum, 1954 Szendi, 1956, etc.). As the names indicate, the tumour is generally considered to arise from the remains of the mesonephros and might occur in all the parts of the genital canal where the mesonephric duct has previously been located.

The information published on the incidence of clear cell adenocarcinoma is inconsistent. Kent & McKay (1960) reported a series of 2 530 ovarian tumours collected over a period of 48 years in which nine (0.4%) of the tumours were of this type. Twenty-two primary adenocarcinomas of the cervix which included four tumours of this type were analysed by Pomerance & Mackles (1962). Clear cell adenocarcinomas in the vagina have generally been reported as isolated cases.

The age distribution in ovarian tumour series ranges according to Schiller (1939) from eight months to 69 years. McGee et al. (1962) collected from the literature 37 cases of clear cell adenocarcinoma of the cervical region in which the patients were from 13 to 71 years. Judging by the literature, vaginal clear cell adenocarcinomas also seem to have been found in patients of almost any age. Stroink (1947) reported it in a patient aged one year Plate (1950) in a two-year-old and 60-year-old patient, Marlalek (1942) in a patient aged 10 months, and Szendi (1956) in one aged 44 years. Novak and his co-workers (1954) reported eight patients aged from 14 months to 76 years. Case 1 in Tellum (1954) report was 64 years old.

There are very few special characteristics in the clinical picture of ovarian tumours of this type. Parker et al (1960) generally found in their own cases only a palpable mass in the patient's pelvis. In addition, an elevated sedimentation rate was recorded regularly in the cases not given any treatment before admission to hospital. Irregular bleeding, according to the literature, occurs almost without exception in tumours of the cervical canal and examination generally discloses a tumour at the external os. In



Fig 1 (case 1). Cystic clear cell adenocarcinoma of the vagina. Atypical columnar epithelium is seen on the inner surface of the cyst outside it is a zone of inflammatory cells, and clear cell type adenocarcinoma tissue Van Gieson, ×71

vaginal tumours also postcoital or other irregular bleeding has been stated to be the most typical symptom

A typical feature of the histological picture is cells with clear cytoplasm which form bands or border tube-like structures, small acini or alveolar sinuses. Papillary structures are common. Another structural type displays sinuses in which the epithelium bordering them forms pseudopods which were interpreted by Schiller as incomplete glomerular imitations. The former type with clear cytoplasm, is usually called clear cell adenocarcinoma of Saphir and Lackner while the latter is known as Schiller's mesonephroma The former is practically analogous with Grawitz's tumour histologically There is still no unanimity regarding the histogenesis. Schiller (1939) and Novak et al. (1954) believe that this tumour originates from the remnants of the mesonephric duct, regardless of its localisation in the genital canal The conclusion drawn by Teilum (1954) in his extensive study is that histologically highly multiform mesonephric tumours, with which he also associates adenomatoid tumours, may arise not only from the epithelial remnants of the mesonephros but also from primitive mesoderm in the neighbourhood of the mesonephric duct Plate (1962) came to the same conclusion. Scully & Barlow (1967) thought that clear cell adenocarcinoma of the ovaries may originate from the Mullerian duct and would thus have to be regarded as a variant of endometrioid carcinoma

Four tumours classified as being of this type, one in the ovary two in the cervical canal and one in the vagina, have been encountered at the Central Hospital of North Carelia since it opened, i.e. between 1953 and 1968 As the clinical experience of these tumours is still meagre, and their histogenesis controversial and as they may present difficulties of histopathological diagnosis, we decided to publish this report because we feel that every new case adds something to our limited knowledge of these tumours. The original paraffin blocks were available for all the cases. New sections were made and they were stained by van Gieson's method.

CASE REPORTS

Case 1 (Journal no 1904??/57)

The patient was a pastor's wife of 37 para VII, who was admitted on January 4 1957 She had had regular menses, most recently on January 15 For previous two months the patient had noted something projecting from the vagina. Nothing abnormal was found at a general medical examination. Her sedimentation rate was 25 mm/h, haemoglobin 13.0 g/100 cc, and a catheter specimen of urine showed no abnormality A stool specimen revealed diphyllobothriasis. Vaginal examination disclosed an egg-sized cyst which projected from the left lateral wall of the lower portion of the vagina. The cervix was normal, the uterus was of normal size, mobile, and the ovaries felt normal. The cyst was removed completely on January 25 1957 and was found to contain reddish clear fluid. Microscopic examination showed some atypical columnar epithelium on the inner surface of the cyst. Deeper in the wall invasive carcinoma was seen it formed solid islets of various sizes. Highly atypical glandular imitation was also demonstrated in places. The tumour tissue consisted of large pale cells rich in cytoplasm, with nuclei displaying strong polymorphism and numerous mitotic figures. The tumour was classified



Fig (case 1) Tumour cell clusters inside the lymphatics. Van Gieson, 223

as clear cell adenocarcinoma (Fig. 1). Clusters of tumour cells were encountered also within the lymphatics (Fig. 2).

The patient was sent to the Department of Obstetrics and Gynaecology of the University Central Hospital, Helsinki for radiotherapy. She was given a total of 5 200 mg. hours of radium therapy and a dose of 2 900 R of deep X-ray treatment. In August 1957 her sedimentation rate varied from 90 to 124 mm/h and symptoms suggestive of brain metastases appeared. The patient died at the end of the same month, on August 28 1957. The autopsy findings are unfortunately not available to us.

Case 2 (Journal no. 110519/65)

The patient was a worker's wife aged 57 para IV. She had had regular menses and menopause at the age of 51. She visited the gynaecological outpatient department for the first time in 1963 when partial prolapse of uterus and a small erosion of the cervix were diagnosed. The erosion was treated by electrocoagulation, and the operation for prolapse (kolporrhaphia ant.+ amputatio cervicis kolpoperineorraphia) was performed some later in 1964. The next time the patient attended for an examination was on June 2, 1965 because of bleeding for about a week. Her sedimentation rate was 30 mm/h, haemoglobin 11.8 g/100 cc. The margin of the external os was hard and slightly blood-stained, the uterus was mobile and small and the ovaries felt normal. A cervico-vaginal smear was reported as Papanicolaou class I. Biopsy specimens were also taken from the cervix and uterine cavity. The histological picture was dominated by a violent, partly necrotizing inflammation. Some giant cells of foreign body type were seen among the inflammatory cells (Fig. 3). In some specimens attention was attracted by very profuse round cells with clear cytoplasm in which the cell contours were distinct, the cytoplasm finely granular and the nuclei slightly irregular (Fig. 4). These cells were first regarded as macrophages and they formed in many places continuous, solid masses which did not, however, present distinct glandular structures. The histological picture was interpreted as atypical, granulomatous inflammation. The



Fig. 3 (case 2). Granulation tissue and a giant cell of foreign body type. Van Gieson, 223.

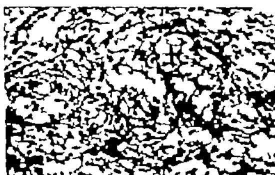
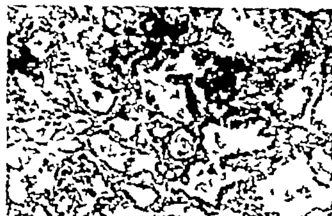


Fig. 4 (case 2). Solid tumour tissue of clear cell type. Van Gieson, 170.

blood-stained discharge recurred and the patient was admitted on December 5 1965. Examination revealed a crater like ulceration with firm edges in the vault of the vagina. Malignant disease was suspected. Biopsy specimens taken from it exhibited a histological picture of the same type as the first specimens, and the great number of foam cells was again a striking finding. During the following three months numerous specimens were taken from the margin of the ulcer and the histological picture remained throughout similar to that described above. The cervico-vaginal smear on January 22, 1966 was reported as Papanicolaou' class III, chiefly because of the dyskaryotic nuclear changes. As the case was still regarded histologically as inflammatory and the clinical picture resembled that of a malignant ulcer, several pathologists in Helsinki were consulted and shown the preparations. It was suggested that the foam cells might be tumour cells characteristic of adenocarcinoma, but no definite decision between these two alternatives, atypical inflammation and clear cell adenocarcinoma, could be made. The patient was observed at short intervals. Her sedimentation rate was between 25 and 35 mm/h, the cervico-vaginal smear finding was consistently Papanicolaou class II. Escherichia coli and enterococcus were grown from the pus taken from the cervical ulceration, but culture for tubercle bacilli and the guinea-pig test were negative. An examination in March 1966 showed that the ulceration had decreased, in April dysuria due to urinary coliform infection was diagnosed. The ulceration was found to have healed in June. There was still a urinary tract infection in August and medication with nitrofurantoin was prescribed. The patient was not seen again until November 22, 1967 when she attended the urological outpatient department with complete urinary retention, at that time her sedimentation rate was 17 mm/h. No ulceration was now seen in the vault of the vagina. Cystoscopy revealed a sharp bend in the urethra. Intravenous urography disclosed pronounced hydronephrotic changes bilaterally in the pelvicalyceal system of the kidney and, on the left, also hydroureter. Micturition cystography showed a diverticular dilatation in the cranial part of the urethra. Its walls were not clearly demarcated and there was marked re-



F g 5 (case 4). Tumour tissue of Schiller s mesonephroma type Van Gieson, x 68

tention in the bladder The conclusion reached was that the patient had a bilateral terminal ureteral obstruction and urinary tract infection. A cystoureteroneostomy was performed on January 19 1968, and marked bilateral hydroureters were found. When the urinary bladder was opened a plate-like induration, which obviously enclosed the uret ric orifices, was found in its neck. The biopsy specimens taken from the induration displayed exactly the same histological picture as before. Foam cells again predominated. It began to appear probable that they were after all tumour cells, and the case was now diagnosed as clear cell adenocarcinoma which had spread from the cervical area to the neck f the bladder but was still of fairly low grade malignancy The patient was given postoperative roentgen therapy 100 R in all, and was followed at intervals of a few months. Almost constant urinary tract infection was diagnosed, but no definite progression was seen in her disease. From No ember 1968 she complained of pain in the perineal region, and urinary incontinence started in January 1969 At the most recent follow-up xamination, March 13, 1969 the urinary incontinence was worse, there was still pain in the perineum, the sedimentation rate was 45 mm h, haemoglobin 11 1 g 100 cc, serum creatinine 0 6 mg/100 cc Gynaecological examination showed the ure thral orifice to be reddish and an rea f induratı n wi a small fistula in it was detected in the centre of the anterior ginal wall. The cervix was no longer isible the uterus was small and mobile the parametria soft. The patient was admitted for therapy with cytotoxic drugs although their fficacy was regarded as uncertain.

Case 3 (Journal N 360529 65)

The patient was a worker wife ged 3 She had been treated earlier for anaemia t the Department f In rnal Medicine of this hospital. Her mense had been regular menarche at the age of 15 She had had three spontaneous deliveries, ymptoms f pre-eclampsia in connection with the first and se ond deli ery and had been sterilized t the third pregn ncy for mental retardation. The gynaecological xamination performed at the time revealed mild cervicitis and the cervico- aginal smear was classified as Papanicolaou class I

The patient was admitted on October 1, 1968, because of constant bleeding which had persisted for well over a month. Examination disclosed a cauliflower-like bleeding tumour which filled the upper half of the vagina. The corpus uteri was normal, with an extensive infiltration palpable on both sides in the parametria. Microscopic examination of the biopsy specimen revealed adenocarcinomatous tissue which was rich in cells and grew in large islets. The cells ere large and contained profuse cytoplasm which was clear and vacuolized, and the histological picture was highly typical of adenocarcinoma. The patient was referred to the Department of Radiotherapy University Central Hospital, Helsinki, where she was given radium, a total of 7 ? mg-hours, the dosage to the agina being 5 400 mg-hours. In addition, she received X-ray treatment. At the examination performed on December 30, 1968, the cervix appeared to contain residual tumour and the patient was therefore given a further course of radium, two doses totalling 4 200 mg-hours. She was examined most recently on March 3 1969 when her subjective condition was good, the upper part of the vagina was slightly contracted, the cervix was smooth but somewhat reddish and there was some discharge from the cervical canal. The uterus was small, mobile, dextroposed. The right lateral parametrium was shortened and smooth, the left one completely soft. Nothing indicative of a recurrence of the carcinoma was seen and the cervico-vaginal smear finding wa Papanicolaou s class II.

Case 4 (Journal No. 0104 4 57)

The patient was a houseowner wife aged 56. She had had regular menses, no pregnancies, menopause at ? years and had been previously treated at the Department of Internal Medicine for low back ache and urinary tract infection. Nothing abnormal had been found at the gynaecological examination performed at the time The patient was admitted on February 13 1957 because she had been are for about five months of an abdominal mass which xtended up to the umbilicus. Gynaecological examination showed the agina and cervix t be healthy but in the abdominal ca ity there a tumour of limited mobility which extended to the level of the umbilicu and it obviously arose from the

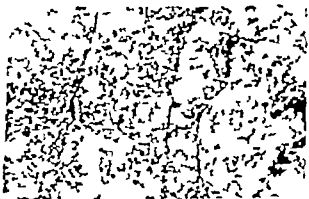


Fig 6 (case 4) Clear cell type tumour tissue Van Gieson, 68

ovary. The patient's sedimentation rate was 19 mm/h, haemoglobin 11.7 g/100 cc. Supravaginal amputation of the uterus and bilateral salpingo-oophorectomy were performed on February 15, 1957. A cystic tumour 20 cm in diameter with a broad pedicle was seen to arise from the left ovary and extend to above the umbilicus. It was partly adherent to the intestine. There was brownish, turbid fluid and a few loose, soft pieces of tumour tissue inside the cyst. Microscopy of the tumour tissue showed a picture in which the predominant feature was perhaps tubular structures typical of Schiller's mesonephroma (Fig. 5). The epithelium bordering them formed numerous small, papillary pseudopods. In addition, there were papillary structures and abundant tissue typical of clear cell adenocarcinoma (Fig. 6). The patient was given postoperative X-ray treatment and attended regularly for follow-up examinations. She still had low back ache and symptoms of urinary tract infection, but remained asymptomatic as regards the tumour for the duration of the 10-year follow-up period.

DISCUSSION

Mesonephric carcinoma, whether of clear cell or another type, is rare in all parts of the genital canal. Of the 954 ovarian tumours diagnosed at the Central Hospital of North Carelia in 1953–1968 one (0.1%) was of this type. Five cases of primary adenocarcinoma of the cervical canal were encountered in 1964–1968, the lifetime of the Pathological Laboratory of our hospital. Two of them were of the clear cell type. We are unfortunately not aware of the incidence of primary tumours of the vagina at our hospital.

The histopathological diagnosis of the so-called mesonephric carcinoma generally causes no difficulties provided the existence of this tumour is remembered. Case of the present series was, however, an exception. A violent inflammatory reaction interfered with interpretation of the histological picture. Clear cells were well-differentiated and did not form a distinct glandular structure and they were therefore regarded at first as macrophages. The dissemination of the process to the neck of the urinary bladder after an asymptomatic period of almost 1 1/2 years in histologically similar form to that at the beginning of the disease was, we believe, evidence of the correctness of the classification of the case as clear cell adenocarcinoma.

There is some disagreement as to whether Schiller's mesonephroma and Saphir and Lackner's clear cell adenocarcinoma are two different tumours or only differing histological manifestations of mesonephric carcinoma. Novak et al. (1954) and Sharan et al. (1967) found both components in the same tumour and advocated the latter theory. It is impossible for us to be sure on the basis of these cases whether these types of tumour derive from remnants of the mesonephric duct or not. We can merely say on the strength of our case 4 that Schiller's mesonephroma and clear cell adenocarcinoma are obviously two different histological manifestations of the same tumour and may also occur in combination in the same tumour. The view that these tumours originate from remnants of the mesonephric duct must obviously be regarded as theory which still awaits final confirmation. This requires evidence in serial sections of a definite connection between the tumour tissue and the remnants of the mesonephros.

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REFERENCES

Hameed, K.: Amer J Obstet Gynec 101: 954, 1968.
Kent, S. W. & McKay, D. G.: Amer J Obstet Gynec 80: 430, 1960.
Marlalek, J. C.: Gynaecologia 7: 13, 1942.
McGee, C. T., Cromer, D. W. & Greene, R. R.: Amer J Obstet Gynec 84: 358, 1962.
Novak, E., Woodruff, J. D. & Novak, E. R.: Amer J Obstet Gynec 68: 1222, 1954.
Parker, T. M., Dockerty, M. B. & Randall, L. M.: Amer J Obstet Gynec 80: 417, 1960.
Plate, W. P.: Gynaecologia 130: 203, 1950.
— Geburtsh Frauenheilk 23: 417, 1963.
Pomerance, W. & Mackles, A.: Amer J Obstet Gynec 84: 367, 1962.
Schiller, W.: Amer J Cancer 35: 1, 1939.
Scully, R. E. & Barlow, J. F.: Cancer 20: 1405, 1967.
Sharan, J., Sahay, U. & Mukherjee, A. K.: Indian J Path Bact 10: 208, 1967.
Stroink, M.: Ned Tydschr Verl 47: 264, 1947.
Sornik, B.: Wien Klin Wschr 44: 875, 1956.
Teilum, G.: Acta Path Microbiol Scandinav 34: 431, 1954.
Tóth, F., Csömör, S. & Mészáros, J.: Amer J Obstet Gynec 88: 452, 1964.

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PLAZENTALOKALISATION MIT VERSCHIEDENEN METHODEN

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Abstract. Seit 1966 wurden bei 104 Patienten für die Lagebestimmung der Plazenta Angiographie, Scintigraphie, Ultraschallmessung und Thermographie vergleichsweise angewandt. Die Scintigraphie wurde in allen Fällen ausgeführt, Angiographie in 29, Ultraschallmessung in 62 und Thermographie in 49 Fällen. Die angiographische Methode ergab in allen Fällen eine korrekte Lokalisation der Plazenta. Sie scheidet aber aus Strahlenschutzgründen für die Routine aus. Die Scintigraphie war in dieser Untersuchung ebenso zuverlässig. Die geringe Strahlenbelastung der Patienten wird von uns nicht als eine Kontraindikation gegen die Anwendung der Methode angesehen. Die Scintigraphie wird daher von uns als die Methode der Wahl für die Plazentalokalisation angesehen, besonders bei der Anwendung kurzlebiger Radionuklide und moderner Apparatur. Die Thermographie und die Ultraschallmessung ermöglichte mit der in dieser Untersuchung angewandten Technik in ca. 70% der Fälle eine richtige Lokalisation der Plazenta. Auf Grund der erwähnten Voraussetzungen kommt den beiden Methoden zur Zeit im Vergleich mit der Scintigraphie doch nur eine untergeordnete Bedeutung zu.

Bei Blutungen im letzten Drittel der Schwangerschaft und bei geplanter Amniotomie ist die Lagebestimmung der Plazenta für den Geburtshelfer eine Voraussetzung für sicheres therapeutisches Handeln und daher von grosser klinischer Bedeutung.

Eine sichere Methode zur Lagebestimmung der Plazenta ist die Beckenarteriographie mit Darstellung der Plazentagefässe im Röntgenbild. Bei ap- und seitlichen Aufnahmen ist eine dreidimensionelle Lagebestimmung möglich. Nach Borell (1968) wurde bei 160 Beckenarteriographien in 98 der Fälle die Plazenta richtig lokalisiert. Leider ist die Strahlenbelastung von Mutter und Foetus relativ hoch, und die Methode wird deshalb nur noch bei dringender klinischer Indikation ausgeführt wenn andere Bestimmungsmethoden keine sichere Aussage zulassen.

Die Scintigraphie erlaubt ebenfalls sehr sichere Aussagen über die Plazentalage (Larson & Nelp, 1965)

Neben diesen beiden Methoden wurden in den letzten Jahren Ultraschallmessungen und Thermographie auf ihre Verwendbarkeit für die Plazentalokalisation erprobt. Ultraschalluntersuchungen können ausgeführt werden mit Hilfe der Scanner Technik (Sundén, 1969 Kohorn et al., 1969) sowie der vereinfachten Methode, wobei das Dopplerprinzip angebracht ist (Bishop 1969).

Um die Treffsicherheit alle dieser Methoden mit einander zu vergleichen, wurde seit Juni 1966 bei Patienten mit Verdacht auf eine Plazenta praevia und bei geplanter Sectio caesarea, wenn möglich, eine Scintigraphie, Ultraschallmessung entsprechend dem Dopplerprinzip und Thermographie sowie in speziellen Fällen auch eine Angiographie ausgeführt.

MATERIAL UND METHODEN

Seit Juni 1966 wurden insgesamt 104 Patienten untersucht. Alle wurden scintigraphiert, bei 29 wurde eine Angiographie, bei 62 eine Ultraschallmessung und bei 49 eine Thermographie zur Lagebestimmung der Plazenta ausgeführt.

In 37 Fällen konnte die Lage der Plazenta operativ bestätigt werden. Bei 16 Patienten lag eine Plazenta praevia vor. Bei diesen Patienten wurden die übrigen Untersuchungsmethoden zur operativ festgestellten Plazentalage korreliert. Die Resultate für die 16 Praeviafälle sind in Tabelle I und die der übrigen 21 in Tabelle II zusammengefasst. Bei einer dritten Gruppe von 21 Patienten lagen angiographische Befunde für den Vergleich mit anderen Methoden zu Grunde (Tabelle III). Bei den

Tabelle I. *Vergleich der übrigen Methoden mit der operativen Lagebestimmung. Fälle mit Plazenta praevia*

Pat. Nr	Grav. Woche	Szintigraphie	Angiographie	Ultraschall	Thermographie
1	41	+			
2	33	−	+		
3	34	+	+		
4	38	+	+		
5	37	+	+	−	
6	31	−			
7	24	+	+		
8	40	+	+	+	
9	30	+	+	+	
10	30	+	+	+	+
11	33	+		+	+
12	33	+		+	
13	36	+		+	−
14	35	+		+	+
15	28	+			+
16	34	+			

+ = richtig lokalisiert, − = falsch lokalisiert.

restlichen 46 Fällen dienten die szintigraphischen Befunde als Vergleichsgrundlage.

Die Beckenarteriographie wurde nach Einführung eines Teflonkatheters in die Aorta mit Injektion von 40 cm³ 60%-ig U ografin ausgeführt. Normalerweise wurden 4 ap-Bilder das letzte mit Stereo hergestellt.

Die Szintigraphie wurde in den meisten Fällen mit 70 μCi ¹³¹J-markiertem Humanserumalbumin ausgeführt.

Tabelle II. *Vergleich der übrigen Methoden mit der operativen Lagebestimmung. Keine Plazenta praevia-Fälle*

Pat. Nr	Szintigraphie	Ultraschall	Thermographie
17	+	−	
18	+		
19	−		−
20		−	
21			−
22	−		−
23	−	+	
24			−
25			
26			
27	−		+
28		−	−
29	−		
30	−	−	
31			
32		−	−
33			
34			
35			−
36			
37			−

+ = richtig lokalisiert, − = falsch lokalisiert.

Tabelle III. *Vergleich der übrigen Methoden mit der angiographischen Lokalisation*

Pat. Nr	Szintigraphie	Ultraschall	Thermographie
38	+		
39	+		
40	+		
41	+		
42	+		
43	+	−	
44	+	+	
45	+	+	
46	+	−	+
47	+	+	
48	+	+	
49	+	−	
50	+	−	
51	+	+	
52	+	+	
53	+	−	+
54	+		
55	+	−	
56	+		
57	+	+	
58	+		

+ = richtig lokalisiert, − = falsch lokalisiert.

In dieser Form hält sich das Radionuklid sehr lange in der Blutbahn und gestattet die Darstellung des Blutgehaltes in der Plazenta. Vor der Untersuchung wurden Schilddrüse und Speicheldrüsen des Patienten mit Lugolischer Lösung blockiert. Die Untersuchung wurde Std. nach der Injektion und nach Entleerung der Blase ausgeführt. Während des letzten Jahres wurde in vielen Fällen ⁹⁹ᵐTc-Albumin angewandt (mit Perchlorat blockiert). Bei Anwendung von ¹³¹J-markiertem Albumin wurden Punktmessungen an verschiedenen Stellen des Abdomen in Rückenlage und danach in Seitenlage auf der Seite der höchsten Aktivität ausgeführt.

Nach Injektion von 500 μCi ⁹⁹ᵐTc-Albumin wurde die Patientin in Rücken- und Seitenlage szintigraphiert. Für die Untersuchung wurde ein Nuclear Szintigraph mit einem 3 Kristall und einem fokusierenden Kollimator angewandt. Die Szintigraphie wurde als strichförmiges Szintigramm in Skala 1 : 3 gedruckt (Abb. 1 und 4). Gleichzeitig wurden alle Informationen in einem Bandspeicher gelagert für eine weitere Bearbeitung mit Aktivitätsverminderungen. Das Szintigramm wird in ein Photo des Patienten skalengetreu hineinkopiert (Abb. 2).

Überempfindlichkeitsreaktionen nach Injektion der Radionuklide wurden nicht beobachtet. Die Untersuchung dauerte ungefähr Std. was in einigen Fällen beschwerlich für die Patientin war.

Die Ultraschallmessungen wurden mit einem Doptone-ger 1R ausgeführt. Z Piezo Kristalle sorgten für Sendung und Empfang der Schallwellen mit einer Frequenz von ungefähr MHz entsprechend einer Effektintensität von ungefähr 8 mW cm. Dieser Effekt liegt unter dem Energiebereich in welchem Zellschäden beobachtet wurden. Wärmeeffekte entstehen erst bei einer Grössenordnung von 1 W cm

Der Ultraschall wird an Flächen mit unterschiedlicher Schallimpedanz reflektiert. Wenn die reflektierende Schicht sich im Verhältnis zum Detektor bewegt, entsteht ein Dopplereffekt. Die durch diesen verursachte Frequenzänderung wird zu einem akustischen Signal umgeformt.

Bei der Plazentalokalisation erhält man einerseits reflektierende Schallwogen von der Nabelschnur und andererseits von der Plazenta. Dies bedingt einen zusammengesetzten Schalleffekt, der teils aus einem intermittenten, ziemlich hochfrequenten Geräusch synchron mit dem Herzschlag des Foetus und teils aus einem mehr kontinuierlichen *Geräusch* niedrigerer Frequenz besteht „Plazentageräusch". Bei der Plazentalokalisation wird der Ultraschall an vielen Stellen über dem Abdomen senkrecht zur Haut gemessen, wobei man versucht, das Plazentageräusch von verschiedenen Richtungen her einzupeilen. Der Doptone-Sensor ist auf eine Tiefe von 15 cm fokusiert.

Die Thermographie wurde in einem thermostatregulierten Raum mit einer Temperatur von 18°C nach 10 Minuten langer Abkühlung der Patientin in entkleidetem Zustand vorgenommen. Die Untersuchung wurde von vorn und in seitlichen Drehungen im Stehen oder Liegen ausgeführt.



Abb. 2. Skalengetreue Photokopie eines Plazentaszintigramms. Die Plazenta liegt rechts vom Nabel. Die Aktivität im oberen Teil des Szintigramms liegt in der Leber.

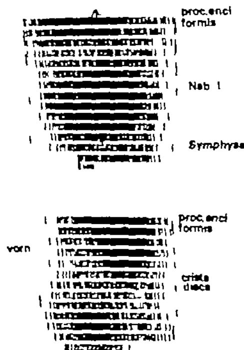


Abb. 1. Szintigramm der Plazenta mit ^{131}I markiertem Humanserumalbumin. (*a*) In Rückenlage, (*b*) in rechter Seitenlage. Die Plazenta liegt tief, vorn und etwas links von der Mittellinie.

Der von uns verwendete Thermograph vom Typ Bofors T... ist mit einem Indiumantimonid Halbleiterdetektor ausgerüstet, der eine unmittelbare Darstellung des Wärmebildes auf einem Bildschirm, auch bei Bewegung der Patientin, ermöglicht.

Im Thermogramm treten die wärmeren Hautbezirke als helle Flecke hervor. Da die Plazenta ein stark durchblutetes Organ ist, stellt sie eine Wärmequelle dar, die, wenn nicht zu tief unter der Haut gelegen, durch Erwärmung der benachbarten Hautbezirke im Thermogramm als warmer Bezirk hervortritt. Die hierbei beobachteten Temperaturdifferenzen zur Umgebung schwanken von 0,5–?°C (Abb. 3 *a* und *b*).

Zur Beurteilung der Lagebefunde wurde das Abdomen in 6 Felder unterteilt, davon drei über und drei unter dem Nabel. Oft war es unmöglich, die Lokalisation eindeutig auf ein Feld zu begrenzen, weshalb sich viele Angaben auf zwei Felder bezogen. Beim Vergleich verschiedener Untersuchungsmethoden wurde eine Übereinstimmung nur akzeptiert, wenn die Angaben in wenigstens einem Felde übereinstimmten.

RESULTAT

Die Resultate der Untersuchung sind in drei Tabellen zusammengefasst. Tabelle I enthält 16 operativ lokalisierte Plazenta praevia-Fälle, die alle szintigraphiert wurden. 8 der Patienten wur

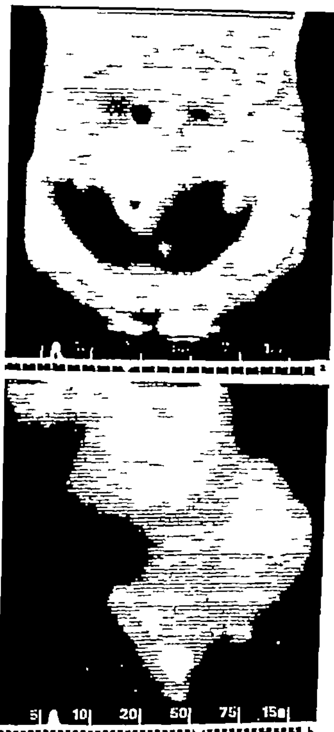


Abb 3 Thermogramm zur Bestimmung der Plazentalage mit eingelegten Isothermen (em). (*a*) Von orn. Höchst Temperatur in den Leisten, in Höhe des Nabels und recht da on. Die schwarzen Flecke in Höhe und ober halb des Nabels entsprechen den Markierungspunkten. (*b*) Von rechts. Deutliche Wärmeerhöhung in Höhe des Nabels. Die Plazenta *liegt* rechts und orn.

den mit *Angiographie 8 mit Ultraschall und 5* mit Thermographie untersucht. Die Angiographie und Ultraschallmessung gestattete in allen untersuchten Fällen eine korrekte Lagebestimmung. Mit der Szintigraphie und Thermographie wurde je ein Fall falsch diagnostiziert. Der szintigraphisch falsch gedeutete Fall war einer der ersten und technisch unbefriedigend untersuchten Patienten (Tabelle I)

In der zweiten Gruppe waren 21 Patienten szintigraphiert und alle wurden richtig gedeutet. 3/11 thermographische Diagnosen waren falsch, ebenso 4/9 Ultraschallmessungen (Tabelle II).

In der dritten Gruppe von 21 nicht operierten Patienten wurde die Angiographie als Ausgangspunkt für den Vergleich mit den übrigen Methoden gewählt. Alle Patienten wurden szintigraphiert und richtig gedeutet. Zwei Patienten wurden thermographiert und richtig lokalisiert. 5/13 Ultraschallmessungen wurden falsch diagnostiziert (Tabelle III).

In der vierten Gruppe wurden 46 Patienten szintigraphisch untersucht. Mit diesen wurden 3 Ultraschallmessungen und 31 Thermographien verglichen. Hierbei stimmten 13/32 Ultraschallmessungen nicht mit der Szintigraphie überein und ebenfalls 7/31 der Thermographien. Ausser dem konnte auf Grund zu kleiner Temperatur differenzen in 5 Fällen keine thermographische Diagnose gestellt werden. Die Unsicherheit der Thermographiemethode bei *12/31* Fällen war also ebenso gross wie die der Ultraschallmethode

DISKUSSION

Die Anzahl der mit den verschiedenen Methoden untersuchten Patienten ist sehr unterschiedlich. Eine Szintigraphie wurde in allen Fällen ausgeführt Beckenarteriographie in ung fähr 30 Ultraschallmessungen in ca. 60% und Thermographie in ca. 50%. Die Ursachen hierfür sind organisatorische und waren dadurch bedingt, dass die verschiedenen Apparaturen nur zeitweise zur Verfügung standen Di relativ klein Patientanzahl in jeder Vergleichsgruppe lässt nur sehr vor sichtig Schlussfolgerungen zu. Die von uns vor genommene Aufteilung in verschiedene Gruppen war jedoch notwendig um im *Einzelfall* einen möglichst sicheren Ausgangspunkt für die Beurteilung *der verschiedenen Lokalisationsbefunde* zu haben. A priori wurde hierbei die operative *Lagebestimmung als die sicherste Methode* angesehen und danach in Übereinstimmung mit Litteraturangaben die angiographische Methode und die Szintigraphie Diese Annahme wurde auch durch

die Untersuchung bestätigt. Die Übereinstimmung zwischen operativer szintigraphischer und angiographischer Lokalisation war nahezu 100%-ig. Wenn auch die Ultraschallmethode in der Gruppe der Praeviafälle in allen untersuchten Fällen eine korrekte Lokalisation ergab, war die Treffsicherheit im Gesamtmaterial doch nicht grösser als 70% ähnlich der der thermographischen Untersuchungen. Die Unsicherheit dieser beiden Methoden ist physikalisch und messtechnisch bedingt.

Die Möglichkeit einer Lagebestimmung der Plazenta durch Thermographie ist abhängig von dem Abstand der Plazenta zur Bauchhaut. Da die Plazenta eine relativ grosse Wärmequelle ist, liegt die maximale Tiefe in der sie noch diagnostiziert werden kann, schätzungsweise in 5—6 cm. Daraus ergibt sich, dass die Lokalisation nur bei vorn oder seitlich gelegener Plazenta möglich ist, während sich die hinten gelegenen Fälle dem thermographischen Nachweis entziehen. Hinzu kommt, dass die thermographische Diagnose im Bauchraum erschwert ist, da oberhalb des Nabels durch die Asymmetrie der Bauchorgane keine Vergleichsmöglichkeiten zwischen rechts und links bestehen. Das Wärmerelief der Haut ist in dem hormonstimulierten Zustand der Gravida oft auch sehr unregelmässig und schwer beurteilbar. Aus diesen Gründen sind die Möglichkeiten der Thermographie für eine sichere Lokalisation der Plazenta begrenzt. Die in dieser Untersuchung erreichte Anzahl richtig gestellter Diagnosen 32/48 (66%) deckt sich ungefähr mit der anderer Untersucher (Jonsson, 1966; *Reynolds, 1967*). *Unseren Erfahrungen nach* wird die Thermographie, auch in geübter Hand, aus oben genannten Gründen in vielen Fällen unsicher sein, weshalb ihr im Vergleich mit sichereren Methoden für die Lokalisation der Plazenta nur eine untergeordnete Bedeutung zukommt.

Die Ultraschallortung ist eine sehr einfache und schnell auszuführende Technik, die an keine grosse Apparatur gebunden ist und keine Katheterisierung oder Injektion von Radionukliden bedingt. Auch hier ist eine Lokalisation der an der Hinterwand gelegenen Plazenta aus physikalischen Gründen schwer. Ebenfalls kann die Lageortung einer sehr oberflächlich gelegenen Plazenta schwierig sein wegen der Fokusierungstiefe des Sensors (15 cm).

Bei einem eindeutigen Untersuchungsresultat ist sowohl die Ultraschallmethode wie auch die Thermographie genügend zuverlässig, und man kann sich mit einer der Methoden begnügen. Die oben erwähnte Unsicherheit in 30% der Fälle ist jedoch zu gross, um die Methode als alleinige Lokalisationsbestimmung vorschlagen zu wollen, insbesondere in Kliniken in denen Angiographie und Szintigraphie ausgeführt werden können. Diese beiden Methoden sind ohne Zweifel die sichersten Methoden für die Lokalisation der Plazenta. Beide exponieren jedoch Mutter und Foetus für ionisierende Strahlung; die Beckenarteriographie doch in ungleich höherem Masse. Die Strahlendosis beläuft sich bei einer angiographischen Untersuchung mit zwei Bildern auf ca. 1–2 rad. Wenn auch die Strahlenempfindlichkeit des Foetus in der zweiten Schwangerschaftshälfte geringer ist, handelt es sich doch um eine Ganzkörperbestrahlung und das Risiko für somatische und genetische Schäden ist schwer abzuschätzen. Aus diesen Gründen wird die Angiographie nur noch in Ausnahmefällen unter dringender klinischer Indikation angewandt. Die Strahlendosis bei der Szintigraphie ist abhängig von dem verwandten Radionuklid. Bei [131]J-markiertem Serumalbumin beträgt sie bei einer injizierten Aktivität von 20 µCi ca. 50–300 mrad. Bei Verwendung von [99m]T oder [113m]In-Albumin beträgt die Dosis < 10 mrad. Diese Dosis ist praktisch ohne Bedeutung und entspricht ungefähr der Gonadendosis bei einer gewöhnlichen Röntgenuntersuchung der Lungen. Ein Nachteil der jetzigen Untersuchungstechnik ist die relativ lange Untersuchungszeit von ca. 30 Minuten für ein Szintigramm in einer Ebene. Diese kann etwas verkürzt werden bei Anwendung hochaktiver kurzlebiger Radionuklide, wesentlich aber nur bei Anwendung einer Gammakamera. Mit dieser ist eine Untersuchung in zwei Ebenen in ca. 15 Minuten möglich.

LITERATUR

Bishop, E. H. The obstetric uses of ultrasound. J. I. Fed Gyn Obstet 4, 190, 1966.

Borell, U. Obstetrik och gynekologi 4, 135 pp. (Schwedisch). Universitetsforlaget, Lund, 1968.

Gershon-Cohen, J. Haberman-Brueschke, J. D. & Brueschke, E. Medical thermography: A summary of current status. Radiol Clin N Amer 3 403 1965.

Gordon, H. Placental localization. The present position. Mod Trends Obstet 1969 257 pp.

Gros, Ch., Walter, J. P. & Dellenbach, P. Indications respectives de la thermographie placentaire et de la

radiographie du placenta. Colloque International de thermographie médical. J Radiol 48 no. 1–, 1967
Hunt, K. M. Placental localization using the Doppler fetal pulse recorder J Obstet Gynaec Brit Comm 76 144 1969
Johnson, Ph. M., Bragg, D & Sciarra, J Placental localization. A comparison of radiopharmaceutic and thermographic methods. Amer J Roentgen 96, 681 1966.
Kohorn, E. L., Walker R. H. & Morrison, J Placental localization. A comparison between ultrasonic compound B scanning and radioisotope scanning. Amer J Obstet Gynec *103* 868, 1969
Larsson, S. & Nelp, W. Visualization of the placenta by radioisotope photoscanning using Technetium ^{99m}-labelled albumin. Amer J Obstet Gynec *93* 950 1965
McAfee, J Stern, H., Fueger G Baggish, M., Holzman, G & Zolle, J ^{99m}Tc-labeled serumalbumin for scintillation scanning of the placenta. J Nucl Med *5* 936, 1964.
Reynolds, W. Thermoplacentography Radiology *89* 8–5 1967
Ryan, J Thermography Australian Radiology *13* –3 1969
Scheer K., Heep, J Maier Borst, W Lorenz, W Sinn, H. & Krauss, O. Placentographie mit kurzlebigen Radionukliden. Nuclearmedizin *8* 15 1969
Schreiber M. & Reid, D Placentography Radiol Clin N Amer *51* 47 1967
Sundén, B. Ultrasonic Placentography Acta Obstet Gynec Scand *48* 161 1969

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RECURRENT FIBROMYOMA OF THE VAGINA

A Case Report

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Abstract This report describes case of recurrent fibromyoma of the vagina. The symptomatology of the condition is indicated and the literature is reviewed.

Most of the benign tumours of the vagina are cysts of different origin, inclusion cysts from Gartner duct remnants, a "blind ureter" or urethrocele. Solid tumours of the vagina are rare.

Fibromyoma f the vaginal wall is a rare condition and since it was first reported in 1733 by D ny de Leyden less than 250 cases have been recorded. In a study f 47 500 gynaecologic specimens, Wharton (1947) found 260 vaginal tumours, of which only 38 (14.6%) were of the solid benign type, and out of these four were classified as myomas. I an extensive survey of solid tumours of the vagina Riedel (1964) found that only 4.5% consisted of fibromyomas. Most authors use the term myoma to include fibromyoma since pure myomas are extremely rare. Most of the vaginal fibromyomas reported are relatively small varying from 1.5–4.5 cm in maximum diameter. These tumours may however ach tremendou size. Phitaddi (1930) described one ith vaginal fibromyoma which after removal was found to weigh 1 450 g.

Our patient had moderate-sized fibromyoma in th anterior vaginal wall under the urethra which was surgically removed in 1964 due to dysp reunia and feeling of oppression in the lower abdomen. I 1969 the patient developed large tumour in the same location which was removed due to dyspareunia.

CASE REPORT

Mrs E. M. 33 years old and III-parous, when she first attended the department of gynaecology in 1964, complaining of dyspareunia and occasional discomfort in the lower abdomen, mainly during her premenstrual periods. Menstruation was regular with normal flow. Her previous history was negative.

Pelvic examination showed an ovoid soft mass about the size of walnut, bulging from the anterior vaginal all in the suburethral area and covered by an intact vaginal mucosa. The cervix, uterus and appendages were normal. An intravenous pyelogram and cystoscopy were normal. The tumour was easily enucleated through longitudinal incision in the anterior vaginal wall. The tumor as solid but soft in consistency and presented on dissection a gray-white appearance. Histological examination revealed a fibro-leio-myoma with no evidence of degenerative or malignant changes (Fig. 1).

In March, 1969 the patient was examined anew because of complaints of increasing dyspareunia. The examination showed submucosal soft vaginal mass about the size of hen egg in the same location as in 1964. The cervix, uterus and appendages were normal. A needle aspiration of the tumour was performed, but no fluid could be obtained. The patient was operated on and the tumour was shelled out without difficulty (Figs. 2 and 3). The postoperative period as uneventful.

The tumour had maximum diameter of 5.5 cm and as soft but solid and showed gray-white appearance on dissection. Histopathological examination showed a highly differentiated fibroleio-myoma without signs of malignancy (Fig. 4).

COMMENTS

As fibromyoma of the agina is rare, this condition has often been primarily diagnosed as cystocele, vaginal cyst, urethrocele or cancer.

Recurrent benign fibromyoma of the vagina seems to be extremely rare and we have only been able to find one case in the literature (Marcos, 1966).

V ginal fibromyomas generally occur in parous women between the ges of 35 and 50. The

radiographie du placenta. Colloque International de thermographie médical. J Radiol 48 no. 1-., 1967
Hunt, K. M., Placental localization using the Doptone fetal pulse recorder J Obstet Gynaec Brit Comm 76 144 1969
Johnson, Ph. M., Bragg, D & Sciarra, J Placental localization A comparison of radiopharmaceutic and thermographic methods. Amer J Roentgen 95 681 1966.
Kobori, E. L., Walker R. H & Morrison, J Placental localization. A comparison between ultrasonic compound B scanning and radioisotope scanning. Amer J Obstet Gynec 103 868 1969
Larsson, S. & Nelp, W Visualization of the placenta by radioisotope photoscanning using Technetium ⁹⁹ᵐ labelled albumin. Amer J Obstet Gynec 93 950 1965
McAfee J Stern, H., Fueger G Baggish, M., Holzman, G & Zolle, I ⁹⁹ᵐTc-labeled serumalbumin for scintillation scanning of the placenta. J Nucl Med 5 936, 1964
Reynolds, W., Thermoplacentography Radiology 89 825 1967
Ryan, J Thermography Australian Radiology 13 .3 1969
Scheer K., Heep, J Maier Borst, W Lorenz, W Sinn, H. & Krauss, O Placentographie mit kurzlebigen Radionukliden. Nuclearmedizin 8 15 1969
Schreiber M & Red, D Placentography Radiol Clin N Amer 51 47 1967
Sundén, B., Ultrasonic Placentography Acta Obstet Gynec Scand 43 161, 1969

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Fig. 4 Histologic section of the fibroleiomyoma operated in 1969 with the same appearance as the specimen from the operation in 1964.

dyspareunia and a feeling of oppression in the lower abdomen.

Other patients with the same location of the tumour have been reported to experience difficulty and or frequency of urination.

In some cases a protruding mass constituted the patients chief complaint. Degenerative changes in the fibromyoma can occur with ulceration of the adjacent mucosa and these cases are usually primarily diagnosed as carcinoma or sarcoma of the vagina. In association with pregnancy difficulty in labour has been encountered with large vaginal fibromyomas. There seems to be no correlation between the occurrence of vaginal fibromyomas and fibromyomas of the uterus. Nürnberger (1930) reviewed 130 cases of vaginal fibromyomas and only 10 were found to have associated fibromyomas of the uterus. Vaginal fibromyoma is regarded as a benign tumour and sarcomatous changes have only been reported in a few cases.

REFERENCES

Banerjee, R. J Indian M A 49 181 1967

Bennett, H. G. & Ehrlich, M. M. Am J Obstet Gynec 42 314, 1941

De Leyden, D. cited by Tourneux, J. P. Progr Med Paris 41 1509 1934

Lerude, M. J. & Loeffler F. E., Am J Obstet Gynec 92. 74, 1965

Marcus, J. L. J Obstet Gynaec Brit Comm 73 1013, 1966

Moghissi, K., Obst & Gynec 18 360, 1960.

Nürnberger L., Handbuch der Gynäkologie, edn. 3 Veit Stoeckel, Munich, 1930.

Petroddi, A. Clin Obst 32. 396, 1930.

Quan, A. & Rambaran, S. J. Obstet Gynec 18 360, 1961.

Riedel, H. Zbl Gynäk 86 1497 1964.

Schonberg, L. A., Oliver R., Borks, N. & Derman, G. H.: Obstet Gynec 22 234, 1963

Schrum, M. Obstet Gynec 12 195 1958.

Sjövall, A. Nord Med 53 498, 1955

Wharton, L. R., Gynecology edn 2. Saunders, Philadelphia, 1947

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Fig 1 Histologic section of the fibroleiomyoma operated in 1964.

growths are usually single and over 50% occur in the anterior vaginal wall. The next commonest site is the posterior wall and the least common the lateral wall The aetiology of the condition is uncertain but embryonal remnants and local artery musculature are possible origins of the tumour

The only symptoms our patient showed were



Fig 2 Preoperative view showing the protrusion of the tumour into the vaginal lumen.



Fig 3 The vaginal mucosa opened, exposing the tumour

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SURVIVAL AND HORMONAL RESPONSIVENESS OF ENDOMETRIAL CARCINOMA IN ORGAN CULTURE

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Abstract. Explants from endometrial carcinomas survived well in organ culture during the period studied (7–8 days). The glandular architecture was similar to that in the original carcinomas. Outgrowth in the sponge matrix of cells was correlated to the degree of survival of the primary explants. Stromal disappearance was a common feature. Progesterone greatly impaired the survival, this effect being dose dependent. Estradiol potentiated the effect of progesterone, particularly with respect to less well differentiated carcinomas. The hormonal effects were histologically different from those obtained during in vivo experiments by other observers, who administered systemic progestogens to patients with endometrial carcinoma, but were similar to those obtained after intracavitary administration of progestogens. It is believed that the cytostatic effect is a more relevant factor for the evaluation of progesterone effects on tumour growth than are signs of increased differentiation, since secretory vacuoles could be seen also in cultures not treated with the hormone.

Nordqvist, in a preliminary report (1964), described a method for organ culture of human endometrial carcinoma. All 11 tumour specimens survived well for 7 or 8 days on a sponge matrix (Leighton, 1951) in Parker 199 with 10% adult human blood donor serum. Various sex hormones were added to the cultures. Estrone 15 μg/ml and progesterone 8 μg/ml were noted to reduce survival slightly. Progesterone 80 μg/ml produced advanced or total degeneration in 9 out of 10 specimens. Androsterone 25 μg/ml markedly affected the survival in 3 out of 11 tumours. It was felt that the differentiation of the tumour specimens could change during culture, although the well-known fact that the degree of differentiation can vary considerably within the same tumour was taken into consideration.

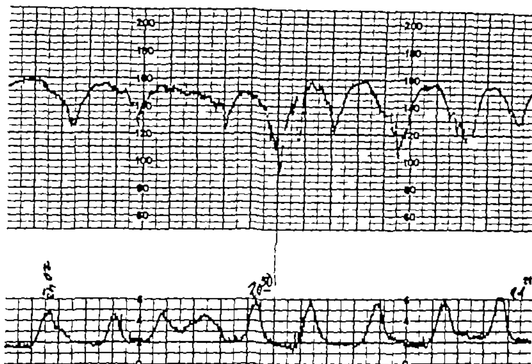
It was suggested that hormonal effects on endometrial carcinoma are the result of direct action on the tumour cells, that most endometrial carcinomas can regress on progesterone treatment providing concentrations high enough can be achieved in the tumour tissue, and that different carcinomas need different concentrations of the hormone in order to respond.

In a recent study Kohorn & Tchao (1968) reported on 10 endometrial carcinomas studied in organ culture. Tumour pieces on Millipore filters were placed in agar enriched with medium 199 and 10% calf serum. After 3–4 days in culture, results were obtained closely resembling those reported by Nordqvist (1964). It was believed that improved differentiation of the explants, noted in 6 out of 8 carcinomas treated with progesterone 10 μg/ml, was of greater importance in predicting the responsiveness to progestogens of individual carcinomas in vivo than the marked inhibition of survival of the explants noted after progesterone 50 μg/ml.

The mode of action of progesterone and progesterone-like compounds on endometrial carcinoma is still largely unknown. Little is also known about various factors that perhaps influence the hormonal response, e.g. age, parity, degree of differentiation, and hormonal concentrations. Thus further experimental work seems to be necessary. In this paper a continued study of the hormonal response of endometrial carcinoma in organ cultures will be presented. The method used is a slight modification of that published earlier (Nordqvist, 1964).

MATERIAL AND METHODS

47 endometrial adenocarcinomas, obtained by curettage from randomly chosen and previously untreated women,



Curves like these report foetal heart conditions in a high-risk pregnancy

This cardiotocogram was plotted by the hp 8020 foetal monitoring system. The upper part presents foetal heart frequency which can be derived either from the heart sound or ECG. The lower part presents labour activity which can be derived either from an external tocometer or from an intra-uterine catheter.

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Cardiotocograph based on research by Dr K. Hammacher

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MEDICAL INSTRUMENTATION













Fig. 1. Tumour 115. Grade I carcinoma. Original preparation. Appr. × 100.

Fig. 2. Tumour 155. Culture treated with estradiol 20 µg/ml. [illegible] survival. Stroma degeneration. Appr. × 165.

Fig. 3. Tumour 15. Culture treated with progesterone 100 µg/ml. [illegible] survival. Low inactive epithelium. Stroma degeneration. Appr. × 165.

Fig. 4. Tumour 177. Control culture. [illegible] survival. Marked vacuolization at the periphery of the explant. Stroma degeneration. Appr. × 100.

Fig. 5. Tumour 109. Control culture. + + outgrowth with tendency to gland-like arrangement of the epithelial cells. Appr. × 100.

Fig. 6. Tumour 118. Culture treated with prednisolone 50 µg/ml and estradiol 10 µg/ml. 0 outgrowth. Probably initial outgrowth and subsequent degeneration. Appr. × 100.

igs. 1–3). Mitoses were sometimes present although never abundant. The central glands and stromal cells frequently became inactive or degenerated. This was particularly the case in larger explants and is most probably due to poor nutrition of the central parts. In smaller explants, no

Table I *Hormonal concentrations when used alone*

Hormone	Concentration (µg/ml)	No. of tumours
17 β-estradiol[a]	20	39
Progesterone[b]	10	9
	50	20
	100	19
SH 582[c]	5	6
	25	15

[a] L. Light & Co Ltd., Colnbrook.
[b] Sigma, St. Louis, Mo.
[c] Schering AG Berlin (19 nor 17 α-hydroxyprogesterone caproate)

have been studied 8 had to be omitted from the material owing to abundant necrosis or fibrosis in the curettage specimens, or because of technical mishaps resulting in degeneration of most cultures in a series. Thus 39 tumours will be accounted for

After curettage the tumour tissue was placed in Tyrode salt solution or Parker 199 at room temperature and transported to the laboratory within 30-60 min. Parts of the specimens were placed in Bouin fixati e in order to serve as a basis for comparison at the later analysis of the sections.

The tissue to be cultured was washed in Parker 199 and freed of blood clots and necrotic elements. It was cut by free hand into small fragments, 1– mm in diameter Two or three such fragment were placed on one piece of gel foam (Spongostan® Ferrosan, Malmö). Two pieces of gel foam were placed in a Carrel flask (D5) containing a medium consisting of 1.5 ml Parker 199 with 0 adult human blood donor serum and 10% chick embryo extract. Antibiotics were added to a final concentration of 60 U benzyl penicillin and 60 µg streptomycin sulphate per ml medium

The flasks were divided into groups, tw in each, to which hormones were added from alcohol stock solutions. The hormonal concentrations used are shown in T bles I and II Alcohol only was added to controls. The final alcohol concentration was 0.67

The flasks were incubated at 37.5°C If necessary the medium in all flasks of a series was hanged after 3-4

Table II *Hormonal concentrations hen used in combination*

17 β-estradiol	Concentration, µg ml: Progesterone	SH 58	No of tumours
20	10		6
10	50		13
20	50		20
20	100		6
20		5	6
20		25	15

days. The gel foam pieces were removed after 7 or 8 days, fixed in Bouin solution, dehydrated, embedded in paraffin-wax, serially sectioned at 5 to 10 µm, and stained with haematoxylin and eosin.

At analysis of the sections, survival as scored according to the following four groups.

+ + + Excellent survival.
+ + Good survival, occasional necrosis.
+ Poor survival, advanced necrosis.
0 No survival.

For every carcinoma, the hormonally treated or control groups comprised t o Carrel flasks ith 4-6 tumour fragments in each. Thus it is probable tha the groups are fairly representati e in the case of heterogeneous carcinomas also Where all fragments in each flask did not survi e equally well, the scoring is based on the best survi ing explants rather than on the a erage survival, because the primary aim of the present investigation as to study the possible cytostatic effect of the added hormones.

The original communication on this method (Leighton, 1951) described the outgrowth of e g mice mammary adenocarcinoma cells in the sponge matrix in a three dimensional way The slides of the present study ere accordingly examined for such outgrowth, hich was scored according to the following three groups

+ + Marked outgrowth, sometimes with gland-like formation.
+ Viable cell present in the ponge matrix.
0 No outgrowth, or degenerated cells in the sponge matrix.

Serial sections ere prepared from the original specimens, initially fixed, as described above for the gel foam pieces. The usually employed system for histological classification of endometrial carcinoma is that of Broders a further elaborated by Mahler (for ref. see Novak & Novak, 1958). According to Kottmeier (1968), the Cancer Committee of F I G O recommend the use of three degrees of grading

Grade 1 Carcinoma, well differentiated.
Grade 2 Carcinoma show ng various degrees of differentiation.
Grade 3 Carcinoma, poorl diff rentiated or anaplastic.

I this material, grades and 3 ha e been considered together because of the few tumours in some of the hormone treated groups The histological and cytological criteria used ar those given by Nov k & Novak (1958). Acanthomatous changes ha influenced the grading only hen pronounced hen they lead to cl sification of the tumours as grade II lesion

RESULTS

Explants with survival score had an actively growing epithelium of th same histological

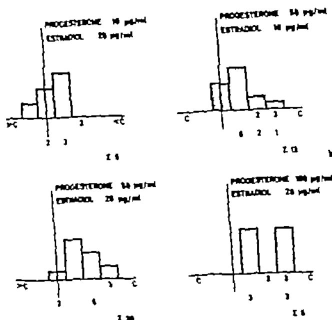


Fig. 8. Survival of endometrial carcinomas in organ culture at different progesterone-estradiol combinations compared with corresponding controls. For details, see text.

not affect survival when given alone nor did progesterone 10 ng/ml (P 10). With increasing concentration of progesterone, however, survival was greatly impaired. The effect of SH 582 also shows a dose-dependent response, although the effects were never pronounced.

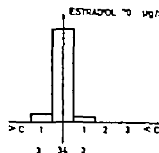
The various groups are quantitatively and qualitatively heterogeneous. It is therefore more relevant to compare the survival in the hormonally treated cultures with that in their own controls. The diagrams in Figs. 7, 8, and 9 are representative of such comparison. The bars illustrate the percentage distribution of cultures surviving equal to, 1 degree better or 1–3 degrees poorer than the corresponding controls, as shown by the numbers below each bar. Further below are given the absolute distribution and the total number of carcinomas treated with given hormonal concentration.

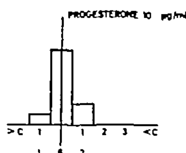
The dose dependent response to progesterone in this comparison is more obvious than when the direct score distribution is studied. E 20 or P 10 has no effect. By an increase of the progesterone concentration to P 50, growth was inhibited in almost half of the tumours. At P 100, only 1 tumour survived equally as well as its control. The mean inhibition score in each hormonal concentration, has been calculated (Table III). Minus signs ( ) indicate inhibition, plus signs (+) better survival than in controls. The hormone treated groups have been compared with the possibility of zero inhibition by means of the *t*-test. The effects of P 50 and P 100 are statistically significant, $0.01 > p > 0.001$ and $p < 0.001$ respectively. The difference between these two progesterone concentrations is also highly significant, $t = 5.7$ at 35 d.f. $p < 0.001$. Furthermore, P 50 combined with E 10 or E 20 significantly reduced the survival.

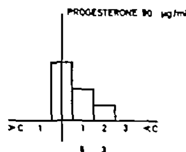
Table III. *Change of survival in hormone-treated groups, compared to corresponding controls*

Mean inhibition score" mean of differences in survival scores of control and hormone-treated cultures of each tumour. *t*-tests performed against 0

Hormone conc. ng/ml	Total number	Mean inhibition score	Stand. error	d.f.	
E 20	39	0.03	0.06	38	0.5
P 10	9	0.11	0.20	8	0.6
P 50	20	0.60	0.17	19	3.5
P 100	19	2.21	0.21	18	10.5
P 10 E 20	6	−0.33	0.33	5	1.0
P 50 E 10	13	1.0	0.25	12	4.0
P 50 E 20	20	−1.5	0.20	19	7.5
P 100 E 20	6	2.0	0.45	5	4.4
SH 5	6	0.50	0.22	5	2.3
SH 25	15	0.13	0.1	14	0.7
SH 5 E 20	6	0	0.37	5	0
SH 25 E 20	15	0.53	0.17	14	3.1







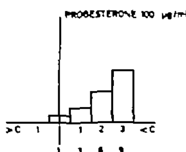


Fig. 7. Survival of endometrial carcinoma in organ culture at different hormonal concentrations compared with corresponding controls. For details, see text.

central degeneration was seen. A common feature seemingly independent of epithelial survival was reduction in amount or disappearance of stromal cells (cf. Fig. 1 and 2). Pronounced reduction of the stroma was seen in 34 of 39 control cultures.

Vacuolization of epithelial cells at the margin of the explants and in the outgrowths in the matrix (see below) was commonly observed in accordance with normal endometrium in organ culture (Ehrmann et al. 1961, Figge 1963) (Fig. 4). Such vacuolization was present in 19 out of 39 controls, and in 19 out of the 28 progesterone-treated cultures (50 and 100 µg/ml) with any viable tissue left after 7 or 8 days in culture.

In explants with survival score + (cf. Fig. 3) pyknosis and necrosis were marked, and remaining viable cells did not proliferate. Vacuoles could be seen. At survival score 0 no viable tissue was left after 7 or 8 days in culture.

Outgrowth in the sponge matrix is demonstrated in Fig. 5. A marked outgrowth with formation of the cell as strands of a single or multilayered epithelium sometimes showing a gland-like pattern, is indicated as + +. Vacuoles were present in outgrowing cells as well as in the periphery of the explants. Mitoses were sometimes present. Outgrowth could be continuous or discontinuous with the primary explant. Out of all 211 cultures (4.2 flasks) + + outgrowth was present in 5. (25).

In 104 cultures (50) seemingly viable cells were present in the matrix either singly or in small groups (+ outgrowth). Whether this is the result of exfoliation of single cells or cell groups or of actual migration from the explant cannot be determined. The cell nests were never large enough to establish a gland-like pattern, nor were they continuous with the explant.

In the remaining 55 cultures (25) classified as 0 outgrowth, one of two patterns could be seen, either no evidence of outgrowth, or degenerated cells present in the matrix which indicated exfoliation of necrotic cells from the explants or initial outgrowth, followed by degeneration. This type was predominantly present in progesterone treated cultures (cf. Fig. 6).

The outgrowth pattern had a close relation to the survival rate of the primary explant: decreasing survival is followed by a decreasing outgrowth. As could be expected the largest statistical significance (p 0.001) is found between survival scores – and . With this correlation in mind, it is of less interest to analyse the effect of the hormones on survival and outgrowth separately.

Survival was – – or + + in all controls. The addition of estradiol 20 µg/ml (E 0) did

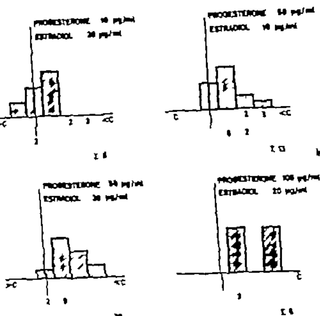


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Table III. *Change of survival in hormone-treated groups, compared to corresponding controls*

Mean inhibition score = mean of differences in survival scores of control and hormone-treated cultures of each tumour. t-tests performed against 0.

Hormone conc. µg/ml	Total number	Mean inhibition score	Stand. error	d.f.	
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P 50	20	−0.60	0.17	19	3.5*
P 100	19	−2.21	0.21	18	10.5**
P 10 E 20	6	−0.33	0.33	5	1.0
P 50 E 10	13	1.0	0.25	12	4.0
P 50 E 20	20	−1.5	0.20	19	7.5**
P 100 E 20	6	−2.0	0.45	5	4.4
SH 5	6	0.50	0.22	5	2.3
SH 25	15	−0.13	0.19	14	0.7
SH 5 E 20	6	0	0.37	5	0
SH 25 E 20	15	−0.53	0.17	14	3.1

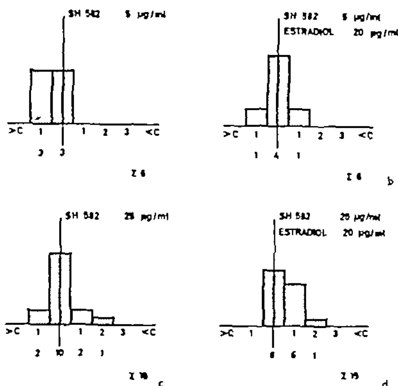


Fig 9 Survival of endometrial carcinoma I organ culture at different concentrations of SH 582, alone or combined with estradiol, compared with corresponding controls. For details, see text.

A comparison of Figs 7 *c* 8 *b* and 8 *c* again suggests an increasing *potentiation of the inhibitory* action of progesterone (P 50) by the addition of increasing *concentrations* of estradiol By statistical analysis, it was evident that E 20 significantly enhanced the inhibitory action of P 50 ($t = 3.5$ at 38 d.f $0.01 > p > 0.001$) but that this was not true for E 10 ($t = 1.4$ at 31 d.f., N S) nor was the difference between the two combined hormone groups statistically significant ($t = 1.6$ at 31 d.f., N.S) P 100 was not potentiated by E 20 (cf Figs. 7 *d* and 8 *d*) This could perhaps be explained by the fact that a *maximum effect is* reached with progesterone alone at this concentration.

SH 5 exerts no effect (cf Fig. 9 and Table III)

At SH 25 survival is possibly reduced (Fig 9 *c*) *although statistically* non-significant (Table III) When E 20 was added the inhibitory effect of *SH 25* is statistically significant (Figure 9 *d* Table III) On the other hand, the difference in the effects of SH 25 alone and combined with E 20 is again non-significant ($t = 1.6$ at 28 d.f NS)

The survival of controls was independent of tumour grade Table IV shows the survival at P 50 alone, and combined with estradiol compared with that of the corresponding controls of grade I and grade II carcinomas. It is evident *that survival is impaired more by the combined* action of the two hormones than by progesterone *alone but also that potentiation of the action of* progesterone by estradiol in vitro is present pram

Table IV *Survival in hormon-treated groups compared with corresponding controls influence of tumour grade*

Tumour grade	Hormone concentration (μg/ml)	Survival C	1	C 2	C 3	C	Total number	Normalized Mean deviation	S E	t-test against P 50
I	P 50	5	4				9	0 44	0 18	
	P 50 + E 10	3	4	1			8	0 75	0 47	0 62 N S
	P 50 + E 20	2	5	2			9	−1 00	0 22	1 97 N S.
II	P 50	6	3	2			11	−0 64	0 24	—
	P 50 + E 10	1	2	1	1		5	−1 40	1 16	0 64 N S
	P 50 + E 20		*4*	*4*	*3*		*11*	*1 91*	*0 25*	*3 66*

arly in carcinomas of low degree of differentiation, i.e. the kind of endometrial neoplastic disease which was less responsive to progestogen therapy in vivo as stated by e.g., Anderson (1965), Kaiser (1960), Kelley & Baker (1960 1965) and Varga and Henriksen (1966).

DISCUSSION

In tissue culture, the effects of physical and chemical agents can be studied at cellular or tissue levels without interference from known or unknown environmental factors present in vivo. It is generally agreed that organ cultures are more prone to retain their structural integrity and functional activity than are cell cultures. Organ cultures are thus more comparable to their parent tissues. To avoid, as far as possible, cellular selection and intracellular alterations, organ cultures are usually limited to short-term experiments, as has been done in the present investigation.

The survival in control cultures after 7–8 days was excellent or good in 83%. In most cases where survival was poor or nil, this could be blamed on the original specimens being necrotic, infected, or fibrous with few viable cancer cells. Röller et al. (1966) reported an overall viability of 43% of 91 surgical specimens of human tumour tissue after 4 7 or 11 days in organ culture. Kalus et al. (1968) in a study of 105 malignant and 55 benign human tumours, found 90% of the cultures viable after 7 days, and 55% after 21 days.

The survival of the explants was markedly reduced when progesterone was present in the medium at concentrations of 50–100 µg/ml. The same observation was made by Kohorn & Tchao (1968). At lower concentrations, 10 µg/ml, the latter authors in some instances noted subnuclear vacuolization of the glandular cells, interpreted as tendency towards improved differentiation of the carcinoma explants. Nordqvist (1964), too, reported that differentiation seemed to have improved in 3 out of 11 carcinomas treated with progesterone 8 µg/ml in organ culture. Although, indeed, in vivo treatment with progestogens can lead to histological changes of endometrial carcinomas indicating improved differentiation (e.g., Bergsjö, 1965 Bonte et al., 1967 Hudson & Stansfeld, 1967 Waterman & Benson, 1967), it is notable that secretory changes appear independently of hormones in organ cultures of normal endometrium (Ehrmann et al., 1961 Figge 1963) and were also seen in the control cultures in the present study. Kohorn & Tchao (1968) believed their findings to be of significance for the prediction of hormonal responsiveness of individual carcinomas in vivo but simultaneously it was reported that survival of the explants was enhanced compared with the controls in 6 out of 10 carcinomas cultured with progesterone 10 µg/ml. Smith et al. (1966) found histological changes in vivo not only in 5 out of 7 carcinomas that clinically showed regression, but also in 3 out of 6 that did not respond clinically to progestogens. Also Varga & Henriksen (1961) stated that despite a benign conversion histologically some carcinomas were no less malignant clinically. Thus, it is the present author's opinion that the growth inhibiting effect of progesterone is the most important feature in evaluating the cytostatic effect of progesterone on endometrial carcinomas in organ cultures.

It is obvious that the effects obtained by administration of progesterone in vitro in the present study are different histologically from alterations achieved by progestogen treatment of endometrial carcinoma in vivo (e.g., Sherman, 1966 Varga & Henriksen, 1966). Possibly the stroma degeneration, seen in the present investigation, prevents the carcinoma cells from responding to progesterone in a way comparable to that in vivo e.g. by secretory activity and also that the relative absence of stroma renders the cancer cells more susceptible to the cytostatic effect of progesterone. However Puckett & Merrill (1967) found vacuolization, pyknosis, and necrosis after orally given Medrogestone. Also the marked degenerative changes obtained by intracavitary administration of progestogens (e.g. Truskett, 1964) deserve special attention in the evaluation of the present in vitro results.

High hormonal concentrations have been used in this study. In the use of other steroid hormones, concentrations ranging from 1–50 µg/ml have been employed in organ cultures (Algard, 1960 Franks & Barton, 1960 Kohorn & Tchao, 1968 Lasnitzki, 1966 Tchao et al., 1968). Figge (1963) found no effects of progesterone, 100 µg/ml, on normal endometrium in organ culture, while Ehrmann (1961) reported complete degeneration after progesterone, 40 µg/ml.

Kullander et al (1966) noted complete degeneration of 9 human mammary carcinomas and 3 out of 7 cervical carcinomas after progesterone 80 μg/ml A non-specific reaction to the hormone was suspected although one mammary gland out of 3 and 4 cervical carcinomas out of 7 survived at the same concentration. No definite arresting effect of progesterone in the same concentration was found on the growth of cell cultures in plasma clots of rat ovarian tumours (Kullander & Källén 1959) In the present study different carcinomas survived to a different degree after P 50 as well as after P 100 A non-specific effect seems unlikely as it should be expected to affect all explants alike

Ehrmann et al (1961) and Figge (1963) believed the effect of progesterone on the endometrium to be exerted via an indirect route. This was partly contradicted by Luginbuhl (1968) Sherman and Woolf (1959) demonstrated that the administration of 17α-hydroxyprogesterone caproate lowered the urinary levels of luteinizing hormone (LH) in patients with endometrial carcinoma originally presenting with elevated LH values. However Kelley & Baker (1960 1961) Varga & Henriksen (1961) and others have claimed that the progestogen effect is direct on the carcinoma tissue The bioassay method described by Hooker and Forbes (1947) the pronounced histological effects on endometrial carcinoma after intracavitarily administered progestogens (Triskett, 1964) and the results of the present study further support the view of a direct action on the endometrium as a principal property of progesterone

ACKNOWLEDGEMENTS

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REFERENCES

Algard, F T Hormone-induced tumors, I Hamster flankorgan and kidney t mor vitro *J N t Cancer Inst 25* 557 1960

Anderson, D G Management f advanced endometrial adenocarcinoma w th medro yprogesterone acetat Amer J Obstet Gynec 92 87 1965

Bergsjö, P *Progesterone* and progestational compounds in the treatment of advanced endometrial carcinom Acta Endocr 49 412, 1965

Bonte, J Lassance, M Drochmans, A & Ide, P Treatment of adenocarcinomas of the uterus ith medroxy progesterone. *In*, Fifth world congress of gynecology and obstetrics (ed. C. Wood and W A W Walters) p. 680 Butterworths, Sydney Australia, 1967

Ehrmann, R. L., McKelvey H. A. & Hertig, A. T Secretory behavior of endometrium in tissue culture Obstet Gynec *17* 416, 1961

Figge, D C. The endocrine stimulation of in vitro endometrium. Acta Cytol 7 245 1963

Franks, L. M & Barton, A. A. The effects of testosterone on the ultrastructure of the mouse prostate in vivo and in organ cultures. Exp Cell Res *19* 35, 1960.

Hooker C. W & Forbes, T R. A bio-assay for minute amounts of progesterone. Endocrinology *41* 158, 1947

Hudson, C. N & Stansfeld, A. G The histological changes produced in untreated adeno-carcinoma of the endometrium by a progestogen J Obstet Gynaec *Brit Comm 74 442, 1967*

Kaiser R., Der cytostatische Effekt verschiedener gestagener Substanzen. *I* Sechstes Symposion der Deutschen Ges. für Endocrinologie (ed. H. Nowakowski) p. 64 Springer Berlin, 1960

Kahn, M Ghidoni, J J & O'Neal, R. M. The growth of tumors in matrix cultures. Cancer *2* 507 1963

Kelley R. M & Baker W H. Clinical observations on the effect of progesterone in the treatment of metastatic endometrial carcinoma. *In*. Biological activities of steroids in relation to cancer (ed. G Pincus & F P Vollmer) *p. 427 Academic Press, New York and* London, 1960

Kelley R. M & Baker W H. Progestational agents in the treatment of carcinoma of the endometrium. New Engl J Med 264 16, 1961

Kelley R. M & Baker W H. The role of progesterone in human endometrial cancer Cancer Res *5* 1190, 1965

Kohorn, E. I & Tchao, R. The effect of hormones on endometrial carcinoma n organ culture J Obstet Gynaec Brit Comm 75 1 6, 1968

Kottmeier H. L Some problems relating to classification and staging of mal gnant tumours in the female pelvis J Int Fed Gynaec Obstet 6 168 1968

Kullander S & Källén, B Studies on the growth of xperimental varian tumours in tissue culture Acta Endocr *32* 41 1959

Kullander S Källén, B & Olivecrona, H Organ culture of human tumours as a tool for evaluation of endocrine sensitivity *I* The S edish Cancer Society Yearbook 1963–1965 (ed H Bergstrand), p. 431 Almqvist & W ksell, Stockholm, 1966

Lasnitzki, I Dingle J T & Adams, S The effect of teroid *hormones on lysosomal activity of rat* ventral prostate gland in culture E p Cell Res *43* 120, 1966

Leighton, J A sponge matri method for tissue culture Formation f organized aggregates of cells in vitro J Nat Cance Inst *1* 545 1951

Laghbuhl, W H Electron microscopic study of the effects of tissue culture on human endometrium. Amer J Obstet Gynec *103* 192, 1968.

Nordqvist, R. S. B Hormone effects on carcinoma of the human uterine body studied in organ culture. A preliminary report. Acta Obstet Gynec Scand *43* 296, 1964.

Novak, E. & Novak, E. R. Gynecologic and obstetric pathology. With clinical and endocrine relations, p. 33. W. B. Saunders Co Philadelphia & London, 1958.

Puckett, T G & Merrill, J. A. Oral progestin therapy for metastatic adenocarcinoma of the endometrium. J Okl Med Ass *60* 306, 1967

Röller M-R., Owen, S. P & Heidelberger C. Studies on organ culture of human tumors. Cancer Res *26* 626, 1966.

Sherman, A. I.: Progesterone cap ate in the treatment of endometrial cancer. Obstet (ec *28* 309 1966.

Sherman, A. I. & Woolf, R. B) endocrine basis for endometrial carcinoma. Amer   Obstet Gynec *77* 233, 1959

Smith, J P Rutledge, F & Soffar, S W Progestins in the treatment of patients with endometrial adenocarcinoma. Amer J Obstet Gynec *94* 977 1966.

Tchao, R., Easty G. C Ambrose, E. J Raven, R. W & Bloom, H J G Effect of chemotherapeutic agents and hormones on organ cultures of human tumours. Europ J Cancer *4* 39 1968.

Truskett, I. D The treatment of endometrial carcinoma by the instillation of a progestational agent. *In.* Symposium on recent advances in ovarian and synthetic steroids. Sydney Australia, 1964.

Varga, A. & Henriksen, E. Clinical and histopathological evaluation of the effect of 17-alpha-hydroxyprogesterone-17-n-caproate on endometrial carcinoma. Obstet Gynec *18* 658, 1961

Varga, A. & Henriksen, E.: Hormonal treatment of endometrial cancer In. New concepts in gynecological oncology (ed. G. C. Lewis, Jr, W B Wentz & R. M. Jaffe), p. 301 F A. Davis Company Philadelphia, 1966.

Wasserman, E. A. & Benson, R. C Medrogestone therapy in advanced endometrial adenocarcinoma. Obstet Gynec *30* 626, 1967

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ESTIMATION OF FETAL MATURITY BY AMNIOTIC FLUID CYTOLOGY

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Abstract. Eighty-three specimens of liquor amnii from the 30th to the 42nd gestational week were examined cytologically by the Nile Blue sulphate method, and the results were compared with earlier investigations. From the 17th week a large increase in the percentage of orange cells was found, expressing fetal maturity. However, it seems that the large number of specimens with a low content of orange cells late in pregnancy makes the method less suitable as a routine method. On the other hand it may be useful in the evaluation of possible placental insufficiency.

An important problem in obstetrics is the exact evaluation of the gestational age and thus of fetal maturity, especially when obstetric management may involve induction of labour or elective Caesarean section.

A number of factors may be used in the determination of the gestational age, such as the menstrual history, information about the time of conception, and the date of the first fetal movements. Moreover, assessment of the size of the uterus and the weight of the fetus, X-ray examination directed against centres of ossification and other parameters, oestriol excretion in urine as well as measurement of the biparietal diameter by ultrasonic scanning may be of value in the estimation. However, all these factors are not completely reliable, and in certain circumstances they may lead to completely wrong and misleading results. A possible exception is ultrasonic scanning, but this requires such expensive and highly developed equipment that, so far, it has not been widely adopted.

Brosens & Gordon (1966) have reported a new method for the evaluation of fetal maturity based on cytological examination of liquor amnii following staining with Nile Blue sulphate, a method first investigated for the diagnosis of ruptured membranes (Kittrich, 1963; Brosens & Gordon, 1965). They found a close relationship between the number of orange cells in the amniotic fluid, expressed in percentages, and the gestational age (Table I), and this relationship has been confirmed by later investigations (Gordon & Brosens, 1967; Brosens, Gordon & Baert, 1969).

This well-defined relationship has not been confirmed completely by other investigators (Hubler, 1967; Jørring, 1968; Sharp, 1969; Chan, Willis & Woods, 1969), for which reason the present authors have found it desirable to re-examine the suitability of the method.

METHOD ✓

One drop of amniotic fluid was mixed directly on a slide with one drop of 0.1% aqueous Nile Blue sulphate, a cover slip applied, and the preparation examined microscopically at × 400 enlargement. Four types of cells were found: (1) blue nucleate cells, (2) blue anucleate cells, (3) achromatic anucleate cells, and (4) orange anucleate cells. Brosens & Gordon (1965) have shown that the anucleate orange cells originate from fetal sebaceous glands, and thus the percentage of these cells can be taken as an indication of sebaceous gland activity and therefore of maturity. In each preparation at least 500 stained cells are counted, and the number of orange cells is expressed in percentages of the total amount. This procedure is easy to learn, cheap, requires no special equipment, and can be completed within 10 min.

MATERIAL

The series comprised 83 specimens obtained by amniocentesis (48) or by hindwater puncture (35), totalling 81 patients in whom the gestational age was not in doubt. 20 of them had pre-eclampsia, 6 hypertension, and 3 oedema. Eight specimens were from patients with placental insufficiency.

Table I *Correlation between the percentage of orange stained cells and fetal maturity* (*Brosens & Gordon, 1966*)

Maturity (weeks)	Orange-stained cells (%)
< 34	< 1
34–38	1–10
38–40	10–50 +
> 40	> 50

RESULTS

Fig. 1 shows the percentage of orange cells in relation to the gestational age It is seen that the percentage was low until the 37th–38th week, when a sudden increase took place However even after that time there was a large number of specimens with a low content of orange cells. Thus, 32 % of the specimens contained less than 10 % orange cells after the 37th week, and in two of these the percentage was zero It should be emphasized that there was no doubt about the maturity of the infants in these cases. The 29 specimens from patients with pre-eclampsia, hypertension, and oedema showed no deviation from the distribution in Fig. 1 The specimens from the 8 patients with placental insufficiency were all from 38th–41st week, and these also showed no deviation from the overall distribution.

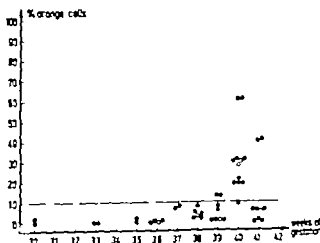


Fig 1 The relationship between the percentage of orange stained cells in the amniotic fluid and duration of gestation. ○ amniocentesis (48), ● hind waterpuncture (35)

DISCUSSION

All investigators have found a considerable increase in the percentage of orange cells after the 37th week, the earliest time of observation of more than 10 % orange cells varying from the 36th to the 38th week However the unreliability of the method stems from the fact that all investigators observed cases of less than 10 orange cells after the 37th week. This percentage of error varied between 6 and 40, in the present material it was 32. This high percentage of error is the most serious disadvantage of the method As an aid to prenatal determination of maturity the method requires amniocentesis, which is another disadvantage as a considerable number of fruitless attempts must be expected as well as a few complications (Burnett & Anderson 1965 Creasman, Lawrence & Thiede, 1968 Peddle, 1968) In this connection the risk of fetomaternal transfusion should be particularly considered, involving a risk of antibody formation with possible consequences for later pregnancies (Peddle 1968). The frequency of this complication can undoubtedly be considerably reduced by routine determination of placental localisation by ultrasonic scanning (Kohorn Walker Morrison & Campbell 1969) as well as by the use of Teflon catheters (Mann, Padawer & Romney 1966) Because of the disadvantages, amniotic fluid cytology cannot be expected to become a routine method of assessment. However in patients with uncertain gestational age particularly in cases of possible placental insufficiency with a small fetus and low oestriol values, the method can be used as a speedy and simple aid in the determination.

CONCLUSION

If more than 10 % orange cells are found in the amniotic fluid, the gestational age is at least 36 weeks, and most likely 38 weeks or more In cases with less than 10 orange cells the gestational age cannot be reliably determined. The method is especially applicable in cases of possible placental insufficiency

REFERENCES

Brosens, I & Gordon, H J Obstet Gynaec Brit Comm 7 342, 1965
— J Obstet Gynaec Brit Comm 73 88 1966

Brosens, I., Gordon, H. & Baert, A.: J Obstet Gynaec Brit Comm 76: 20, 1969.

Barnett, R. G. & Anderson, W. R.: J Iowa Med Soc 58: 130, 1968.

Chen, W. H., Wilbs, L. & Woods, J.: J Obstet Gynaec Brit Comm 76: 193, 1969.

Cassmer, W. T., Lawrence, R. A. & Thiede, H. A.: JAMA 204: 949, 1968.

Gordon, H. & Brosens, I.: Obstet Gynec (NY) 30: 652, 1967.

Huisjes, D. H. J.: Nederl T Geneesk 111: 128, 1967.

Jörring, K.: Nord Med 79: 626, 1968.

Kittrich, M.: Geburtsh Frauenheilk 23: 156, 1963.

Kohorn, E. I., Walker, R. H., Becker Morrison, J. & Campbell, S.: Amer J Obstet Gynec 103: 866, 1969.

Mann, L., Padawer, M. & Romney, S. L.: Obstet Gynec (NY) 27: 497, 1966.

Peddle, L. J.: Amer J Obstet Gynec 100: 567, 1968.

Sharp, F.: J Obstet Gynaec Brit Comm 75: 812, 1968.

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Announcements

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Late afternoons and the morning of the third day Free Communications.

Official languages. Danish, Norwegian, Swedish.

Information. Professor Ingerslev 39 Noerrebrogade, 8000 Aarhus, Denmark

Death

Knaus Herman Vienna Austria, professor and past chairman of the department of obstetrics and gynaecology of the German university in Prague, Czecho-Slovakia, and of the gynaecological department of the Vienna Town Hospital in Lainz, honorary doctor of the Université catholique de Louvain, honorary president of the Austrian Society of Gynaecology and Obstetrics, holder of the title "World Pioneer and Leader of the International Fertility Association" died in Vienna on Aug 22, aged 78

Note

Dr Robert W Kistner ass. clin. prof of obstetrics and gynaecology Harvard Medical School, Boston, has published a very complete book about contraceptive pills, suitable for the public. It is now available in the Swedish language entitled "P piller" published by Bokförlaget Spektra, Halmstad Sweden, and recommendable also to students and practitioners.

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STUDIES ON FETAL CIRCULATION IN LEGAL ABORTIONS

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From the Department of Obstetrics and Gynecology (Head: A. Brosset M.D.), Centrallasarettet Mölndal, Sweden

Abstract. The condition of the fetal circulation after intra-amniotic instillation of 50% glucose solution and extra-amniotic instillation of 20% salt solution has been studied with the aid of an ultrasonic technique. The series consisted of 64 cases of legal abortion. Thirty-six women were given intra-amniotic instillation and 28 women extra-amniotic instillation. In a series, comprising 8 patients, where glucose solution was administered intra-amniotically and the condition of the fetal circulation was recorded every 1/4 hour the latter disappeared, on an average, after about 2 hours. In a series where the fetal circulation was recorded both before and immediately after the intervention, and then only 24 hours later all circulation had ceased after 24 hours. In a series of 7 cases of extra-amniotic intervention, fetal circulation ceased within 1 / hours. In 2 cases it was found to be still intact after 24 hours. In a series of 21 cases where salt solution was instilled extra-amniotically the circulation was found to be intact after 24 hours in 7 cases. In 9 cases abortion had occurred within 24 hours of instillation. In 5 cases recordings were negative.

In the total material comprising 64 cases (36 intra-amniotic and 28 extra-amniotic interventions) fetal circulation could not be detected after 24 hours in all cases where glucose was administered intra-amniotically. Following extra-amniotic instillation, fetal circulation was intact in 9 fetuses. With all the intra-amniotic interventions, abortion was obtained after one course of treatment. Ten of the extra-amniotic interventions were unsuccessful, and a second instillation was given, which resulted in a rapid, successful effect in each case.

On account of the liberal nature of Swedish legislation on abortion, Swedish gynaecologists have been afforded ample opportunities to study problems of scientific and practical interest in connection with interventions of this kind.

During recent years, intra-uterine instillation of hypertonic solutions, given both intra-amniotically and extra-amniotically has been the most usual method for inducing abortion in Sweden.

REVIEW OF STUDIES

The mode of action of these solutions has been subjected to extensive studies. Importance has been attached to the fact that fetal death has been associated with instillation (Fuchs, 1965 Gochberg & Reid, 1966 Wagner 1966). However that abortion can occur even with a living fetus has been shown by Stamm & de Watteville (1954) and Wood et al. (1962), among other investigators. Brosset, (1958), following glucose instillation given in an unknown twin pregnancy was able to show that the fetus had died where the amniotic sac had been punctured, whereas the other fetus had continued to live. The intervention had not achieved the desired result and therefore hysterotomy had been performed.

Great importance has been attached also to the fact that an increase in the volume of the uterus occurs after instillation owing to osmosis (Csapo et al., 1963 Jaffin et al., 1962). Several authors, however have been doubtful about the importance of this mechanism (Bengtsson, 1967 etc.).

Placental injury with the disturbance of hormone production, especially a decrease in progesterone production, has been regarded as the most important factor since progesterone is considered to have a blocking effect on the myometrium (Bengtsson & Csapo 1962). Cassmer (1959) showed that the production of progesterone presupposes a placenta with an intact circulation, and hence a living fetus. Borth (1952), following an intervention for abortion was not able to show any decrease in urinary pregnanediol excretion. Nor did analyses of the progesterone content in the uterine venous blood show any decrease in

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The investigation consisted of two parts. The first comprised 15 cases. Here 8 women were given intra-amniotic and 7 women extra-amniotic instillations. Tables II and III show the distribution by weeks of pregnancy. One of these patients did not abort within 8 days and, consequently renewed intervention proved necessary. Since the fetal circulation persisted, it was possible to make a new study of the destiny of the circulation after instillation.

The other part of the investigation consisted of 49 cases. Here, recordings were made prior to and immediately after instillation and for periods of about / hour. No further observations were made until the next morning, or about 24 hours after the intervention.

For the intra-amniotic instillations 50% glucose solution was used (Brosset, 1958). The amniotic sac was punctured from the abdomen. The maximal amount of amniotic fluid was removed and then replaced by glucose solution in excess. For the extra-amniotic instillations 20% saline solution was used (Svane, 1960). In both cases 500 mg of Terramycin was added to the instillation fluid.

RESULTS

In the first group where 8 women were given glucose solution intra-amniotically the fetal circulation could not be detected after about 2 hours. The time varied between 1 / and 2 1/2 hours (see Table IV).

In the 6 cases where saline solution was injected extra-amniotically two types of result were obtained. In cases 1 and 6, intact circulation could be detected for 3 hours. When listening was resumed 24 hours after instillation, the circulation was still found to be present. In the rest of the cases the circulation ceased after between 1 and hours. In the case where the circulation was found to be present after 24 hours, and where intervention was repeated (case 4) after 8 days, the circulation ceased after 1 / hours (Table V). In the combined series consisting of

Table IV. *Time required for fetal circulation to disappear after intra-amniotic glucose instillation*

Case No	Time (hours)
1	1½
2	2½
3	2½
4	2½
5	1½
6	2½
7	1½
8	2
Mean	about 2 hours

Table V. *Time required for fetal circulation to disappear after extra-amniotic saline instillation*

Case	Time (hours)
1	> 24
2	1½
3	2
4	1½
5	2
6	> 24
7	1
Mean about	1½ hours

Table VI. *Results after 24 hours*

Aborted within 24 hours	25 cases
Auscultation at 24 hours	39 cases
Total	64 cases
Intact circulation	8 + 1 cases
Negative recording	30 cases
Total	39 cases

64 patients, 25 women aborted within 24 hours after the instillation, and here no late record was made. In 9 of the remaining patients who had not aborted, the circulation was found to be intact 24 hours after the intervention (in one case only a few days later). All 9 of these patients had been given salt solution extra-amniotically. In 30 cases the recordings were negative (Table VI).

All patients in this series, on whom intra-amniotic intervention was performed, aborted after one course of treatment. Eighteen patients who were given extra-amniotic instillation aborted after one course of treatment. In 10 patients, instillation was repeated and abortion took place soon after.

CONCLUSIONS AND COMMENTS

With our technique and material, fetal death occurred within 24 hours in all cases following intra-amniotic intervention. Other investigators have reported living fetuses in association with abortion following glucose instillation (Timonen, 1962. Brosset, 1958). With an objective method that is superior to fetal ECG in studies of this type it could be established that there was rapid cessation of the fetal circulation. Transient serious disturbances in rhythm could often be observed. These occurred initially and might subsequently

Table I. *Distribution of cases by gestation period*

Gestation weeks	13	14	15	16	17	18	19	20
Number of cases	*4*	*6*	*19*	*22*	*6*	*1*	*4*	*2*

Table II. *Distribution by gestation in the intra-amniotic intervention group*

Gestation weeks	17	18	19	20	Total
Number of cases	3	1	2	2	8

Table III. *Distribution by gestation in the extra-amniotic intervention group*

Gestation weeks	13	14	15	16	Total
Number of cases	1	1	4	1	7

progesterone production after intervention (Short 1965) On the other hand it was possible to show an increase in sensitivity to oxytocin. However Weist, (1966) using an isotope technique, found a reduction in progesterone production. Samples were taken prior to the intervention, after labour had started, and after the completed abortion. The urinary excretion of estrogen has been studied by Timonen (1962). After intra-amniotic instillation of 50% glucose solution the urinary estradiol content rose, whereas a decrease in the estrone and estriol content was observed. The cause was stated to be severely disturbed metabolism in an injured placenta.

In those cases where saline solution was used, a direct stimulating effect on the myometrium could be established (Wiqvist & Eriksson 1964).

The information in the literature on the effect of hypertonic solutions on the fetus is scanty Fuchs (1967) stated that the fetus died within a few hours following saline instillation. He considered he could draw this conclusion because in two cases where he had performed hysterotomy 2 hours after the instillation he then found dead fetuses. Gochberg & Reid (1966) had asked the mothers when the fetal movements had ceased, and considered that, on the basis of this information he could maintain that the fetuses had died within 2–4 hours after the instillation He had used saline solution. In one case which was followed with fetal ECG recordings all activity disappeared after some minutes. This may possibly be an artefact, as Timonen demonstrated as early as 1962. In a single case, the cessation of activity followed the intervention, but with a resumption after 30 min. Subsequently the activity was irregular for 3 1/ hour and the ECG showed signs of fetal asphyxia. Thereafter the fetal ECG was again quite normal The fetus lived for 4 hours after the intervention, when hysterotomy was performed In a series consisting of seven intra-amniotic instillations of glucose, Timonen found that one fetus was alive when hysterotomy was performed 24 hours after the intervention. Bengtsson & Csapo (1962) reported that fetal death occurred within a few hours of intervention. This was established by the fact that the catheter inserted in the uterus in connection with the intervention ceased to move. In one case hysterotomy was performed 4 hours after the instillation. It was then possible to remove a fetus that had recently died. In all these cases saline solution had been instilled.

It was impossible to find any information in the literature on the fate of the fetus after extra amniotic instillation of saline

In this work the condition of the fetal circulation following intra-amniotic instillation of glucose and extra-amniotic instillation of saline has been studied. Ultrasonic technique was applied.

MATERIAL AND METHODS

The investigation comprises 64 women who underwent legal abortion on sociomedical grounds in accordance with S edish law 36 received intra-amniotic glucose instillation and 28 extra-amniotic saline instillation. The pregnancies were distributed over the following weeks of pregnancy (Table I).

The fetal circulation was studied by an ultrasonic technique. An ultrasonic wav was directed towards the fetus. There the wave is reflected at interfaces and by means of the Doppler effect, fluid movements in the vessels or the heart can be recorded as changed echo frequency I this investigation three different apparatuses were used. Doptone, Sonicaid and Magnaflux. Without the aid of these instruments, which have all proved excellent, an investigation of this kind could not have been conducted. The fetal circulation was carefully identified prior to intervention The optimal position and direction of the probe ere carefully assessed. After the intervention, recording was resumed. The interval between the recordings after the intervention were normally 15 min. Listening as continued until the fetal circulation could no longer be detected. I those cases where the circulation could still be recorded 1 hours after instillation, the latt was discontinued, and was repeated only about 4 hours after the intervention.

Acta Obstet Gynec Scand 49 293–296, 1970

INCIDENCE OF CANDIDA ALBICANS IN WOMEN USING ORAL CONTRACEPTIVES

H. Kålund Jensen, P A. Hansen and Jens Blom

From the Department of Gynaecology and Obstetrics (Head, P Lange M.D) and the Department of Pathology (Head K. Brændes, M.D.), the Central Hospital, Næstved, Denmark

Abstract. An attempt was made to evaluate, by means of culture investigations, the incidence of candida albicans in 276 healthy women of fertile age. The patients were divided into three groups as follows Group P (80 subjects), users of oral contraceptives, groups NP (158 subjects) non-users, group AP (38 subjects), former users. Group P included 15% with candida albicans and 54% with erosion, as against 5% and 24% respectively in group NP The difference in incidence of candida albicans and erosion between groups P and NP is significant at the 5% level. No significant difference was found between groups NP and AP The incidence of candida albicans, trichomonas and erosion is discussed and compared with previous reports.

Since J Stuart Wilkinson, in 1849 published the first report in *The Lancet* on yeasts causing vaginal discharge, several workers have dealt with this subject.

During recent years interest has been focused on candida albicans (c.a.) infections, this being responsible for about 73 to 81% of yeast infections (Ruther et al., 1958). The incidence of infection with c.a. seems to be increasing. Presumably the continuing increased use of broad-spectrum antibiotics and, partly also of steroids, might be a causative factor (Winner & Hurley 1964 Stenderup 1957)

Several more recent reports have described increased incidence of vaginal candidiasis in connection with the use of contraceptives (Walsh, Hildebrandt & Prystowsky 1965 Yaffee & Grots, 1965 Porter & Lyle, 1966 Catterall, 1966 Rieth, 1967 Walsh, Hildebrandt & Prystowsky 1968 Morris & Morris, 1967).

However the series examined are rather limited and consist mainly of women presenting with genital tract symptoms. It has not been possible to demonstrate any significant difference between users and non-users f contraceptives.

For the purpose of further elucidation of the subject, we found it interesting to evaluate the incidence of c.a. in a population group comprising healthy women of fertil age. The series includes both users and non-users of contraceptives.

Own investigations

Data was obtained in connection with a voluntary prophylactic smear investigation of the nursing staff at the Central Hospital in Næstved and includes 276 women of fertile age.

The subjects can be divided into three groups: NP P and AP The average ages in the three groups were 37 32, and 32 years, respectively Group NP consisted of 158 women who had never received hormonal treatment, group P comprised 80 patients using oral contraceptives for contraceptive purposes, and group AP 38 patients who had formerly used oral contraceptives.

METHOD

All patients underwent gynaecological examination, vaginal swabs were taken and examined by culture Yeast culture was made at 37°C on Sabouraud medium containing penicillin and streptomycin. Positive results after 72 hours were sent to the State Serum Institute for more detailed classification of the type of yeast.

In connection with the study "wet" smears were examined by direct microscopy for trichomonas, and gynaecological case history was obtained.

RESULTS

As is shown in Figs. 1 and 2, group NP includes 60 (38%) with trichomonas, 38 (24%) with ero-

disappear It was not possible to determine the developments during the last minutes of the circulation

After the extra-amniotic instillation of saline, the fetal circulation ceased very rapidly in a number of cases in a few it continued even after 24 hours. Scarcely half of these patients aborted spontaneously without further measures on our part. In just over half of the cases we considered that we were justified in giving further instillations. At birth all the fetuses were macerated and thus had died later than 24 hours after instillation. The mechanism causing fetal death in these cases appears to b different from that after intra-amniotic instillation of glucose solution.

Doptone Smith Kline Comp. USA. Sw Rep. Hugo Tillquist. *Sonicaid* Sonicaid Lim. England. Sw Rep Stille Werner *Magnaflux*, Magnaflux Corp. USA. Sw Rep. Allhabo Solna.

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REFERENCES

Bengtsson, L. Ph. & Csapo, A. Amer J Obstet Gynec *83* 1083–1093 1962.

Bengtsson, L. Ph. Svensk Läkartidn *64* 5037–5048 1967

Borth, R., Stamm, O. & de Watteville, H. Acta Endocr *11* 103–110, 1952.

Bromet, A. Acta Obstet Gynec Scand *37* 519–5.5 1958

Cassmer O. Acta Endocr *32* Suppl. *45* 1959

Csapo, A., Jaffin, H., Kerenyi, T de Mattos, C. E. R. & de Sousa Filho, M. B. Amer J Obstet Gynec *87* 89 905 1963

Fuchs, F Fuchs, A.-R., Short, R. V & Wagner G Acta Obstet Gynec Scand *44* 63–70, 1965

Fuchs, F *In* Advances in Obstetrics and Gynecology (ed. S. L. Marcus & C. C Marcus), pp. 258–270 Williams & Wilkins, Baltimore 1967

Gochberg, S. H & Reid, D E. Obstet Gynec *27* 648–654 1966.

Jaffin, H., Kerenyi, T & Wood, E. C Amer J Obstet Gynec *84* 602–608, 196.

Short, R. V Wagner G Fuchs, A R & Fuchs, F Amer J Obstet Gynec *91* 13 136, 1965

Stamm, O & de Watteville H. Gynéc Obstet (Paris) *53* 171–187 1954

S ane, H Danish Med Bull 7 51 54, 1960

Timonen, S., Hirvonen, S. E. & Wickman, K. J Endocr *4* 17 21 1962.

Wagner G. Clin Obstet Gynec 9 570–534 1966.

Wiest, W G., Kerenyi, T & Csapo A. Obstet Gynec *27* 589 1966.

Wiqvist, N E. & Eriksson, G Amer J Obstet Gynec *88* 75–81 1964

Wood, C., Booth, R. T & Pinkerton, J H M Brit Med J 705–709 196.

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disappear. It was not possible to determine the developments during the last minutes of the circulation.

After the extra-amniotic instillation of saline, the fetal circulation ceased very rapidly in a number of cases; in a few it continued even after 24 hours. Scarcely half of these patients aborted spontaneously without further measures on our part. In just over half of the cases we considered that we were justified in giving further instillations. At birth, all the fetuses were macerated and thus had died later than 24 hours after instillation. The mechanism causing fetal death in these cases appears to be different from that after intra-amniotic instillation of glucose solution.

Doptone: Smith Kline Corp. USA. S[illegible] Rep. Hugo Tillquist. *Sonicaid*, Sonicaid Ltd. England. Sw. Rep. Sille-Werner. *Magnaflux*, Magnaflux Corp. USA. Sw. Rep. Allhabo, Solna.

REFERENCES

Bengtsson, L. Ph. & Csapo, A.: Amer J Obstet Gynec 83: 1083–1093, 1962.

Bengtsson, L. Ph.: Svensk Läkartidn 64: 5037–5048, 1967.

Borth, R., Stamm, O. & de Watteville, H.: Acta Endocr 11: 103–110, 1952.

Brosset, A.: Acta Obstet Gynec Scand 37: [illegible]19–525, 1958.

Cassmer, O.: Acta Endocr 32: Suppl. 45, 1959.

Csapo, A., Jaffin, H., Kerenyi, T., de Mattos, C. E. R. & de Souza Filho, M. B.: Amer J Obstet Gynec 87: [illegible]–[illegible], 1963.

Fuchs, F., Fuchs, A. R., Short, R. V. & Wagner, G.: Acta Obstet Gynec Scand 44: 63–70, 1965.

Fuchs, F.: In: Advances in Obstetrics and Gynecology (ed. S. L. Marcus & C. C. Marcus), pp. 258–[illegible]. Williams & Wilkins, Baltimore, 1967.

Gochberg, S. H. & Reid, D. E.: Obstet Gynec [illegible]: 648–654, 1966.

Jaffin, H., Kerenyi, T. & Wood, E. C.: Amer J Obstet Gynec 84: 602–608, 1962.

Short, R. V., Wagner, G., Fuchs, A. R. & Fuchs, F.: Amer J Obstet Gynec 91: 13[illegible]–136, 196[illegible].

Stamm, O. & de Watteville, H.: Gynaec Obstet (Paris) [illegible]: 171–187, 1954.

Stone, H.: Danish Med Bull [illegible]: [illegible], 1960.

Timonen, S., Hirvonen, E. & Wichmann, K.: J Endocr 4: 17–[illegible], 1962.

Wagner, G.: Clin Obstet Gynec 9: 520–534, 1966.

Ward, W. G., Kerenyi, T. & Csapo, A.: Obstet Gynec [illegible]: [illegible]0, 1966.

Wagner, N. E. & Eriksson, G.: Amer J Obstet Gynec 8[illegible]: [illegible]–[illegible]41, 1964.

Wood, C., Booth, R. T. & Pinkerton, J. H. M.: Brit Med J [illegible]: 7[illegible]–7[illegible]9, 1962.

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The last-mentioned type of yeast ppeared in 8 cases of group NP (5%), the same incidence as c.a.

Thirteen of the 25 subjects with c.a. complained of at least two of the following symptoms: itching, feeling of dryness and vaginal discharge. Three of them had clinical demonstrable vaginitis. During the study none of the 25 subjects was pregnant, suffered from endocrine disorders or received antibiotics.

By comparing groups P and NP it appears that the incidence of erosion is significantly different ($\chi^2 = 23$, P 99.9) and that the incidence of c.a. shows a significant difference ($\chi^2 = 5.6$, P 97.5) within the 5% level. (There is a pronounced difference as regards erosion, less pronounced for c.a.) There was no difference between groups NP and AP.

The initial cytological study as appears from Table I, revealed 22 subjects with cytological changes, corresponding to 9% of the entire series. Two had tumour cells, 7 presented suspicious cells and, in 13 subjects, atypical cells were revealed. Four of these subjects used oral contraceptives. One of these had suspicious cells and 3 had atypical cells.

The histological terminology applied is that suggested by Clemmesen (Clemmesen, 1962).

Table I. *Results of cervical and vaginal cytology in 276 fertile women*

Tumour cells	Suspicious cells	Atypical cells	Normal cells
2	7	13	254

DISCUSSION

The incidence of c.a. found in the present series corresponds ery well to the incidence reported in the literature (Wisner & Hurley 1964. Thomsen Pedersen, 1967).

Hence, Thomsen Pedersen gives a c.a. incidence ranging from 4 to 10% in non-pregnant, symptomless women, whereas, in women with symptoms referable to the genital tract, the c.a. incidence ranges from 6 to 16%.

In series of 291 women of fertile age nd without any genital tract symptoms, Morris & Morris found 13.5% c.a. in users of oral contraceptives and 9.1% in non-users. As distinct from the present study it was not possible to demonstrate any significant difference between the two groups. In our series 15% c.a. were found in users and 5% in non-users.

Presumably the cause of the increased incidence of c.a. in users of oral contraceptives is to b. found in the effect exerted by oral contraceptives on the concentration of insulin and glucose in plasma (Spellacy & Carlson, 1966) which in its turn influences the vaginal epithelium and the acidity of the vagina (pH).

The incidence of trichomonas infection found in the present series (37–45%) is higher than the incidence stated in the literature (Frederiksberg–Malmö–Lyng). Hence, in the Frederiksberg study (Koch, 1966) and the Malmö study (Bjerre, 1969) trichomonas infection was found in 28% and 10% respectively of women aged 30–45 years.

From a study of 1 413 patients, Lyng (1967) found an incidence of 25.8%. The reason for this discrepancy might be a varying technique and identification.

During the present study wet smears were examined immediately after the specimens were taken. The result was regarded as positive if only one trichomonas parasite was observed.

In the Malmö study dry specimens were studied which explains the low frequency observed in that series.

It is stated in the literature (Morris & Morris, 1967. Mestelt et al. 1968. Bjerre, 1969) that erosion or eversion occurs in 15. 25 and 33% respectively. This incidence corresponds to that found in the present series, 24% in non-users. The somewhat incongruous statements concerning the incidence of erosion given by various workers must be considered in the light of the difficulties in distinguishing between a definite pathological finding and normal variation. Morris & Morris (1967) found significantly higher level in users f oral contraceptives 51% as against 33%. In the present series there is much more pronounced difference, 56% as gainst 24%.

During their study Timonen et al. (1966) found that about 50% of patients with torulopsis glabrata infections had symptoms. None of the 13 subjects with torulopsis glabrata in the present study had any symptoms referable to the genital tract.

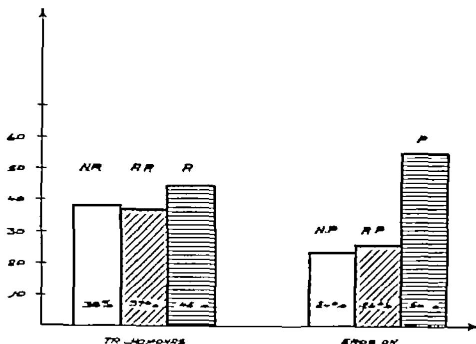


Fig. 1 Incidence of trichomonas and erosion in the three groups, NP AP and P stated as percentage of total

sion, 10 (6.4) with vaginitis, and 21 (13) with yeast infection, 8 of whom (5%) had c.a.

Group P comprises 36 (45) with trichomonas, 45 (56) with erosion, 7 (8.7%) with colpitis, and 15 (19) with yeast infection, 12 of whom (15%) with c.a.

Group AP comprises 14 (37%) with trichomonas, 10 (26%) with erosion, 1 (2.6%) with colpitis, and 8 (21%) with yeast. Five (13) were infected with c.a.

Apart from c.a., the types of yeast found by culture were saccharomyces cerevisiae (3), candida parapsilosis (2) candida quilliermondin (1) and torulopsis glabrata (13)

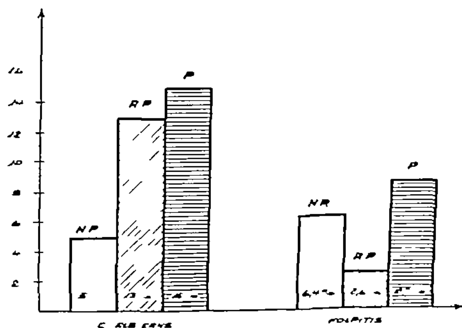


Fig Incidence of candida albicans and vaginitis in the three groups, NP AP and P stated percentage of total

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OVARIAN PREGNANCY

Report of a Case with Lippes's Loop in situ

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Abstract. A case of ovarian pregnancy in a 24-year-old patient, who had been wearing a Lippes loop for about 12 months, is described.

Ovarian pregnancy is rare. Since Spiegelberg, in 1878, set up his criteria for ovarian pregnancy only some 200 cases have been reported. According to Novak & Woodruff (6), Spiegelberg criteria comprised the following items:

1 The Fallopian tube on the affected side must be intact.

2 The foetal sac must occupy the position of the ovary

3 The ovary and sac must be in connection with the uterus through the ovarian ligament.

4 There must be definite ovarian tissue in the wall of the sac.

These criteria have been modified by several authors. For instance, Williams (8) demanded the presence of ovarian tissue in several places of the wall of the foetal sac. Others, including Norris (5), demand microscopic study of the homolateral tube to confirm the diagnosis, but it has been objected (2) that it is unnecessary to remove an otherwise healthy organ.

According to Kern (3) 0.44% of all conceptions result in ectopic pregnancy of which ovarian pregnancies are said to make up 0.7–1.07% (2). The average age in the reported cases of ovarian pregnancy has been 28.7 years, parity 1.3, 27% being primigravidae. The pregnancy has occurred rather more often on the right than on the left side (1.6 : 1).

The most common symptoms and signs are abdominal pain, mass in the true pelvis, and vaginal bleeding, occurring in that order in 95%, 90% and 61% patients. In addition, there may be some normal signs of pregnancy and, in the event of rupture, signs of intraabdominal bleeding and possibly haemorrhagic shock. Thus, the symptoms and signs of ovarian pregnancy do not differ from those of other ectopic pregnancies.

Treatment consists in oophorectomy. A few surgeons remove also the Fallopian tube. About 40% of the patients have exhibited haemorrhage exceeding 750 ml. An embryo has been found in about 41%.

With this background, we felt that the following case history would be of interest:

On March 29th, 1969 a 24-year-old woman was admitted because of sudden abdominal pain and dizziness. There were no known previous attacks.

Gynaecological history. Menarche at 13 years, periods regular 6–7 days/30 days. Two normal deliveries, in 1964 and 1966. A few days after the first delivery gonococci were demonstrated in the infant's ocular discharge, but no signs of infection were found in the mother. She had also not had any pelvic disease, vaginal discharge, or dyspareunia.

Through the past year the patient had been wearing a Lippes loop without complaints.

Last menstrual period started on 15.3.1969 at the expected time. At first, the flow had been as usual, but it continued for two weeks, the last 7 days being scantier. During the 2 days preceding admission there had been no bleeding. There had not previously been any pelvic pain or any symptoms of pregnancy.

On the day of admission, the patient had suddenly vomited and developed severe pain over the lower part of the abdomen. The pain was constant, without radiation, and accompanied by "blackouts" and dizziness. She was taken to the Casualty Ward by a member of her family.

On arrival she was pale and in great pain, hot and dry. B.P. 105/70, pulse rate 80, temperature 37°C, Hb. 79%, ESR 10 mm/hr.

The number of cytological changes found in the present series (22 or 9 %) corresponds roughly to that found by other workers. Hence, Bredahl & Lefèvre (1965) found 5 % in a series of 2 421 subjects, Sjölin (1969) revealed 14 % of 2 055 patients.

Our series did not reveal any relationship between the use of oral contraceptives and cytological changes.

CONCLUSION

I The incidence of candida albicans in the vaginal secretion is higher in users of oral contraceptives than in non-users (15 % as against 5 %). The difference between the two groups is significant at the 5 % level

II The incidence of erosion is considerably higher in users than in non-users of oral contraceptives (56 % as against 24 %) In this case the difference between the two groups is highly significant at the 5 % level.

REFERENCES

Bjerre, B Studies on population screening for early carcinoma of the uterine cervix. Acta Obstet Gynec Scand *48* Suppl. *6* 13 1969

Bredahl, E. & Lefèvre, H. Value of routine cervical and vaginal cytology in gynecological patients in order t detect tumour cells. Acta Obstet Gynec Scand *44* *348, 1965*

Catterall, R. D Candida albicans and the contraceptive pill. Lancet *II* 830, 1966.

Clemmesen, J Epithelabnormiteter på portio Ugeskr Læg *124* 879 1962

Koch, F The population screening for cervical carcinoma in the borough of Frederiksberg 1962 1963 Munksgaard, Copenhagen, 1966.

Lyng, J Vaginal candidiasis. Ugeskr Læg *129* 1051 1967

Messelt, O T Bjelke H., Eker R., Jacobsen, O S., Koller O Kolstad, P Pedersen E. & Schøtt Rivers, E. Mass screening for cancer of the uterine cervi in Østfold County 1959–1965 Report no. 1 from Norwegian Cancer Society 1968.

Morris, C. A. & Morris, P F Normal vaginal microbiology of women of childbearing age in relation to the use of oral contraceptives and vaginal tampons. J Clin Path *20* 636 1967

Pedersen, G Thomsen. Gærsvampefloraen hos Moder og Børn. Universitetsforlaget i Arhus, 1967

Porter P S & Lyle, J S. Yeast vulvovaginitis due to oral contraceptives. Arch Derm *93* 402, 1966.

Rieth, H Candida balanitis and candida fluor after prolonged intake f oral contraceptives. Mykosen *10* *151* 1967

Rüther E., Rieth, H. & Koch, H. Die Bedeutung der Candidamykosen für Gynäkologie in Geburtshilfe. Geburtsh Frauenheilk *18* 1 1958.

Sjölin, K. E. Hvad betyder det cytologiske fund i gynækologie? Ugeskr Læg *131* 1465 1969

Spellacy W M. & Carlson, K. L. Plasma, insulin and blood glucose levels in patients taking oral contraceptives. Amer J Obstet Gynec *95* 474, 1966.

Stenderup, A. Moniliasis. Ugeskr Læg *119* 682, 1957

Timonen, S., Salo, O P Meyer B & Haapoja, H Vaginal mycosis. Acta Obstet Gynec Scand *45* 3, 1966.

Walsh, H., Hildebrandt, R. J & Prystowsky H. Candidal vaginitis associated with the use of oral progestational agents. Amer J Obstet Gynec *93* 904, 1965

Walsh, H., Hildebrandt, R. J & Prystowsky H. Oral progestational agents as a cause f candida vaginitis. Amer J Obstet Gynec *101* 991 1968.

Winner H. J & Hurley R. Candida albicans, 1964

Yaffee, H. S. & Grots, J Moniliasis due to Norethynodrel with Mestranol. New Engl J Med *272* 647 1965

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CAESAREAN SECTION IN CASES OF IMMINENT FOETAL ASPHYXIA

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Abstract. A study was made of 112 cases of imminent foetal asphyxia, delivered by Caesarean section at the Sabbatsberg Hospital 1.1.1966–31.12.1968. As controls 84 cases on which Caesarean section was performed for reasons other than asphyxia were chosen from the same period. A follow-up was made of the children in both groups in order to clarify whether the diagnosis of imminent asphyxia was correct, and if foetuses delivered by Caesarean section for imminent asphyxia developed normally. Of the 112 children with imminent foetal asphyxia 23 had an Apgar score of less than 7 after 1 min. 28 had the umbilical cord wound around the neck in such a way that could explain the imminent asphyxia. At the follow up 25 out of 112 children in the asphyxia group were not normally developed or had physical malformations of some kind. Only 4 infants in the control group had the same signs.

During recent years the perinatal mortality in Sweden has decreased to such an extent, that the death of a child in connection with delivery is regarded as a great failure. Hence the frequency of Caesarean sections in Sweden has considerably increased, especially in cases of imminent foetal asphyxia.

At the University Department of Obstetrics and Gynaecology at the Sabbatsberg Hospital the percentage of Caesarean sections was 2.9% in 1964 and 2.7% in 1965. After that, a remarkable increase was observed. In 1966 the rate was 3.9%, in 1967 4.8 and in 1968 5.3% of all patients were delivered by Caesarean section. The following questions are therefore posed:

1. Has the diagnosis of imminent foetal asphyxia been correct?
2. Will the delivery by Caesarean section of asphyxiated foetuses give normal babies, or those with physical or mental handicap?
3. To what extent is foetal asphyxia caused by malformation or inborn metabolic errors?

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MATERIAL AND METHOD

In order to try to answer the questions raised, a study was made of 112 cases of imminent foetal asphyxia, delivered by Caesarean section 1.1.1966–31.12.1968 at the Sabbatsberg Hospital. As controls, 84 cases on which Caesarean section was performed for reasons other than asphyxia were chosen from the same period, but patients with abruptio placentae and placenta praevia, who had had heavy bleeding before admission to the hospital, were excluded as well as patients with diabetes mellitus and twin deliveries in both groups (Table I).

Foetal distress was diagnosed by systematic recording of the foetal heart rate, and by observation of the amniotic fluid at the time of rupture of the membranes or at amnioscopy. The foetal heart rate was systematically recorded every 15 min, and plotted on a diagram. In this way it is very easy to observe irregularities or continuous decrease or increase of the heart rate. Foetal heart rates below 120/min were considered as decreased, and foetal heart rates above 160 as increased.

In most cases the follow-up was made through the child health centres, where continuous supervision of the children takes place until the age of 3. Most mothers attend the health centres. All unmarried mothers must have a child welfare assistant to their help, who follows the children and, therefore, knows them well. If the mother does not attend a health centre, the child welfare assistant is contacted. In a few cases, where the mother was known to be a well educated and reliable person, she was questioned directly. Some children were sent directly to the paediatric department from the delivery ward, and they were followed up by the paediatricians of the hospital.

At the follow-up the following factors and circumstances were considered: the development in comparison with other children of the same age attending the child health centre; the general health of the children, and the diseases they had had; the age when they were able to sit, to stand up with and without support, when they began to walk, to talk monosyllables and to talk fluently was recorded. The sight and the hearing of the children were also checked.

The distribution of the age of the mothers was similar in both groups (Table II).

The distribution according to parity was similar (Table III).

The abdomen was soft, obese, and tender over the entire lower half. There were no palpable masses.

Gynaecological examination revealed marked tenderness on touching the vaginal cervix and severe tenderness in the entire pelvis, but no masses. The threads of the loop were extruding from the external os.

As the entire picture seemed obscure, it was decided to wait. The B.P and pulse rate became stabilized within the next hour the B.P around 100–105 and the pulse rate at 64–68. Two hours later the B.P was 100 and the pulse rate 80, but at this time there was no doubt of an intraperitoneal haemorrhage. The patient was paler and sweating, the abdomen more protruberant with distal dullness on percussion, and she was complaining of pain in the left shoulder region.

Exploratory laparotomy disclosed about 2 000 ml blood in the abdomen, derived from a ruptured right-sided ovarian cyst, the size of a lemon. The cyst was completely free from the normal Fallopian tube and connected with the uterus by the ovarian ligament. In the ovarian capsule there was a perforation about 2 cm in diameter Right-sided oophorectomy was performed. On the left, the appearances were entirely normal.

When the ovary was cut open, it was found to contain an embryo, about 2 cm in length. Microscopic examination confirmed that this was a primary ovarian pregnancy the foetal sac being diffusely invaded by normal ovarian tissue.

After the patient had received transfusions, the post operative course was uneventful, and she was feeling well when discharged on the 10th day

DISCUSSION

Ectopic pregnancies in association with intra uterine contraceptive devices (IUD) have aroused interest in recent years, and this applies particularly to ovarian pregnancies. According to Tietz. (4) (7) it has been established that a far larger number of ectopic pregnancies in relation to total pregnancies occur among patients with IUD in situ than among others. Moreover it has been found in preliminary studies that among these ectopic pregnancies a striking number are localized in the ovary Among a total of 43 ectopic pregnancies, the Cooperative Statistical Program (USA) found 6 to be ovarian. This gives a ratio of 1 7 while among non users of IUD the ratio was found to be 1 150

The mechanism of the action of IUD is unknown and has been widely discussed Endometrial changes, accelerated passage through the Fallopian tubes, and hormonal changes have been suggested (1) It is difficult to perceive the role of IUD in the development of ovarian pregnancy unless there is something in the theory concerning hormonal changes.

REFERENCES

1 Besch, P K., Boutselis, J G Dettmann, F G No J C., Scott, W P Stevens, V C. & Vorys, N. E fect of intrauterine devices on the normal menstru cycle. Intrauterine contraception *147* Internation Congress series no 86, Amsterdam, New York, Lo don, 1965
2 Boronow R. C., Buckingham, J C., McElin, T W West, R. H., Ovarian pregnancy Amer J Obstet Gyn *91* 1095 1965
3 Kærn, Telt: Extrauteringraviditet på grundlag af københavnsk materiale Nordisk Medicin *41* 406, 19
4 Lewit, S. & Tietze, C Intrauterine contraception: e fectiveness and acceptability Intrauterine contracep tion *95* International Congress series no. 86, Amster dam, New York, London, 1965
5 Norris, C. C., Primary ovarian pregnancy Surg Gyne Obstet vol. 9 1.3 The Surgical Publishing Co. of Chicago, 1909
6. Novak, E. R. & Woodruff, J D Ovarian pregnancy Novak's Gynec Obstet Pathology edn. 6.446, W B Saunders Co., Philadelphia and London, 1967
7 Tietze, C.. Ovarian pregnancies. Amer J Obstet Gynec *101* 775 1968
8. Williams, J W Extrauterine pregnancy Obstetrics *537* Appleton & Co., New York and London, 1903.

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Table VI. *Results of follow-up*

	Dead children	Various malformations	Congenital heart disease	Late development	Small for age	Sleep disturbances
Control group (84)	1	1		2		1
Asphyxia group (112)	1	3	1	11	1	

Delivered before contractions started.

signs of imminent foetal asphyxia are alterations in the foetal heart rate and passage of meconium (Fenton et al., 1962). Bienlarz, Caldeyro-Barcia et al., (1965) stress the importance of so-called dip II, a decrease in foetal heart rate, which remains after the cessation of the uterine contraction, and Saling et al. (1967) consider that intrauterine acidosis is a very important sign of foetal distress. Van Praagh & Tovell (1968) think that low foetal heart rate is the most common sign of foetal anoxia. Foetal heart variations without the passage of meconium in their material were rarely associated with significant distress. They checked the cards of 194 neonates, delivered by Caesarean section because of foetal distress at the Women Hospital, St Lukes Hospital Center in New York during the years 1958–66 and found that only 35 had severe depression at birth. Their figure is in good agreement with the figure found in our series (23 out of 112). The depressed neonates in our material were equally divided between the groups with low heart rate, with rapid heart rate and those who had only passed meconium. The decision to perform Caesarean section on the diagnosis of acute foetal distress seems, therefore, to be very subjective and dependent on the judgement of the individual doctor using the previously stated criteria. For instance, as seen in Table IV the outcome of previous pregnancies seems to influence the doctor' decision. I completely agree with Dyer (1968) who says that it would facilitate the attitude to the problem if more accurately established norms wer available. Continuous monitoring of the foetal heart rate and biochemical supervision of the foetus during labour would be helpful. A number of Caesarean sections in our series probably could have been avoided with better diagnostic methods.

Schneider et al (1967) has made follow-up examination of 44 children to elicit whether there is possible connection between neurologic and/or mental disturbances and prenatal acidosis. They found an aetiologic connection between hypoxia and brain damage. Length of the labour seemed to be less significant than the severity of acidosis. Their study seems to be in agreement with our observation that some children with asphyxia before delivery are not as well developed as the children in the control group.

There also seems to be some connection between previous perinatal death deliveries, and subsequent acute foetal distress during labour 7 out of 56 mothers who had a foetus which developed acute imminent asphyxia with a low heart rate, had earlier had stillborn child. Three of these babies had multiple malformations. The concentration of cases with previously dead children into this group (7 of 9 children) does not seem to be an accidental circumstance. In the control group of 190 patients with normal deliveries only 2 patients had earlier had a perinatal death. One died because of missed transverse position and the other from prolapse of the umbilical cord.

CONCLUSIONS

In summing up this investigation seems to indicate that the methods used to diagnose imminent foetal asphyxia probably are too uncertain to permit an exact diagnosis, and that some Caesarean sections could have been avoided with better methods. Malformations and inborn metabolic errors may in some cases be the cause of foetal asphyxia.

When performing Caesarean section for imminent foetal asphyxia it is not possible to avoid delivering some children with physical and maybe also with mental handicap. A prospective study of the children, now registered as late developers, can help us to evaluate the risk of the mental handicap.

Table I

Contracted pelvis	53
Abruptio placenta	4
Placenta praevia	5
Breech presentation	4
Face presentation	1
Marginal sinus bleeding	1
Prolonged labour	7
Ileus	1
Retinopathy	2
A B C immunisation	1
Psychiatric indication	1
Elderly primipara with long-standing sterility	1
Prolonged pregnancy	3
	84

Table II *Age distribution (per cent)*

	Age, years					
	15–19	20–24	25–29	30–34	35–39	40–
Control group (84)	5.8	20.9	37.2	15.1	14.0	7.1
Foetal distress group (112)	7.1	28.3	31.8	13.3	10.6	8.8

Earlier spontaneous abortions, legal abortions and dead children were recorded. For comparison the same factors were recorded in a group of 190 patients, with normal deliveries, selected at random from the same period (Table IV).

In table V the causes of previous perinatal deaths are recorded.

RESULTS

When evaluating the results it is important to observe that in this study only the foetal heart rate and observations of the amniotic fluid were used to judge whether or not imminent asphyxia existed. Among the 112 children who were delivered by Caesarean section for imminent foetal asphyxia, 23 had an Apgar score of less than 7 after 1 min. They started to breathe only after resuscitation. 29 children in the same series had the umbilical cord wound around the neck and the arms in such a way that it could explain the imminent asphyxia, but only 3 of them had an Apgar score of less than 7. 56 foetuses had a low heart rate, and 41 a rapid or an irregular heart activity and 16 had only passed meconium. The foetuses with a low Apgar score and with umbilical cord complications are equally distributed among the groups.

In Table VI the results of the follow-up are listed.

In the control group, 1 child died 8 days after delivery from an uncertain neurological disease with convulsions, and 12 children are late developers. In the asphyxia group one child died the second day after delivery as a result of a heart defect, and 24 have not developed normally. Concerning the number of children with disturbed development the difference between groups is statistically significant ($P < 0.001$).

DISCUSSION

Foetal distress remains an ill-defined and contro-versial entity (Dyer 1968). The most importa

Table III *Distribution of parity (per cent)*

	I para	II para	Multipara
Control group (84)	69.8	20.9	9.3
Foetal distress group (112)	65.5	18.6	17.8

Table IV *Cases with earlier spontaneous abortions legal abortions and perinatally dead children (per cent*

	Spontaneous abortions	Legal abortions	Dead children
Normal deliveries (190)	10	3.7	1.1
Control group (84)	25	1.2	10.7
Foetal distress group (112)	13.3	4.3	8.8

Table V *Cause of previous perinatal deaths*

Cause of death	Normal deliveries	Control group	Asphyxia group
Prolapse of umbilical cord	1		
Transverse position	1		
Abruptio placentae		1	2
Contracted pelvis		1	
Postmature (stillborn)		2	1
Premature		1	1
Asphyxia		2	
Toxoplasmosis			1
Congenital syphilis		1	
Malformation		1	1
		9	6

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INVESTIGATION OF URINARY PROTEIN AND LACTATE DEHYDROGENASE IN NORMAL PREGNANCY AND IN PRE ECLAMPSIA BY MEANS OF DISC ELECTROPHORESIS

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Abstract. Dialysed, unconcentrated 24 h specimens of urine from 24 normal, non-pregnant women, 28 normal pregnant women and 12 women with pre-eclampsia were examined using disc electrophoresis. The normal pregnant group showed minor variations from the non-pregnant group. In particular, a significantly raised transferrinuria was noticed. The pre-eclamptic group showed albuminuria and transferrinuria, which was significantly greater than in the normal pregnant group, and the transferrin excretion was found to be 26 times as great as in the normal non-pregnant group. U-LDH was inconstant, but the LDH isoenzyme pattern showed a low LDH-I and/or raised LDH-III, IV and V activity. The raised albumin excretion is explained by increased albumin filtration in pre-eclampsia. It is suggested that similar conditions hold true for the excretion of transferrin. The characteristic shift of the LDH isoenzymes is considered to be due to renal ischaemia.

Several investigators previously have examined urinary protein fractions in various pathological conditions of pregnancy.

Investigation of the lactate-dehydrogenase-isoenzymes (LDH-isoenzymes) in normal pregnancy or in pre-eclampsia does not seem to have been published previously and few details are known about the daily lactate dehydrogenase excretion (U LDH) either in normal pregnancy or pre-eclampsia.

Parviainen et al. (1951) found, by the use of paper electrophoresis, that the albumin fraction in the urine of patients with very mild pre-eclampsia was low (25.3–38.8%) whereas the gamma-globulins accounted for between 32.5 and 55% of the urinary proteins. The amounts of beta- and gamma-globulin were highly variable. Increasing severity of pre-eclampsia resulted in an increase of the albumin fraction (55.4–61.9%) at the expense of the other protein fractions.

The last finding is supported by other paper electrophoretic investigations of the urinary proteins in pre-eclamptics, Mack (1955), Niesert (1962). Moreover Niesert showed, by the use of an antitransferrin serum, that there was transferrin in the urine of pre-eclamptic patients and postulated that transferrin accounted for the majority of the beta-globulinfraction. Transferrin could not be identified in normal pregnant urine by the use of antitransferrin serum.

Lorinz et al. (1961), however, found that with increasing severity of pre-eclampsia the urinary excretion of gamma-globulin rose (up to 36.4%). The beta-globulin fraction also rose (18.2%) whereas the albumin fraction fell.

Using immuno-electrophoresis, McEwan (1968), examined the urine of pregnant women with proteinuria due to various causes. In pregnant women, without pre-eclampsia, but with urinary infection, only three fractions (albumin, transferrin and gamma-globulin) could be identified and these disappeared after treatment of the infection. In patients with pre-eclampsia more fractions could be separated, six in mild cases and up to nine in more severe cases. The presence of gamma-A-globulin and gamma-macroglobulin was taken as serious prognostic sign.

The use of the electrophoretic methods mentioned required that the urine examined should be concentrated in all cases.

Excreted U LDH in the urine of normal pregnant women and of pre-eclamptics was inves-

REFERENCES

1 Bieniarz, J. Fernandez Sepulveda, R. & Caldyro-Barcia, R. Am J Obst Gynec 9 871 1965
2 Dyer I Am J Obst Gynec 100 710, 1968.
3 Fenton, A. N & Steer C. M Amer J Obst Gynec 83 354 1962.
4 van Praagh, I. G. L. & Tovell, H. M. M Obstet Gynec 31 674 1968
5 Saling, E. & Schneider D J Obst Gynaec Brit Comm 74 799 1967
6 Schneider D Kulick, S., Haensler H., Vennebusch, H. & Saling, E. Gynaecologia 164 179 1967

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INVESTIGATION OF URINARY PROTEIN AND LACTATE DEHYDROGENASE IN NORMAL PREGNANCY AND IN PRE-ECLAMPSIA BY MEANS OF DISC ELECTROPHORESIS

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Abstract. Dialysed, unconcentrated 24 h specimens of urine from 24 normal, non-pregnant women, 28 normal pregnant women and 12 women with pre-eclampsia were examined using disc electrophoresis. The normal pregnant group showed minor variations from the non-pregnant group. In particular, significantly raised transferrinuria was noticed. The pre-eclamptic group showed albuminuria and transferrinuria, which was significantly greater than in the normal pregnant group, and the transferrin excretion was found to be 26 times as great as in the normal non-pregnant group. U-LDH was inconstant, but the LDH isoenzyme pattern showed a low LDH-1 and/or raised LDH-III, IV and V activity. The raised albumin excretion is explained by increased albumin synthesis in pre-eclampsia. It is suggested that similar conditions hold true for the excretion of transferrin. The characteristic shift of the LDH isoenzymes is considered to be due to renal ischaemia.

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The last finding is supported by other paper electrophoretic investigations of the urinary proteins in pre-eclamptics, Mack (1955), Niesert (196). Moreover Niesert showed, by the use of an antitransferrin serum, that there was transferrin in the urine of pre-eclamptic patients and postulated that transferrin accounted for the majority of the beta-globulinfraction. Transferrin could not be identified in normal pregnant urine by the use of antitransferrin serum.

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The use of the electrophoretic methods mentioned required that the urine examined should be concentrated in all cases.

Excreted U-LDH in the urine of normal pregnant women and of pre-eclamptics was inves-



Fig. 1. Protein pattern and LDH-isoenzymes in urines from normal, non-pregnant women (*right*), normal pregnant women (*middle*) and patients with pre-eclampsia (*left*) after disc electrophoresis on polyacrylamide gel.

tigated by Baier et al. (1965) and Santoni et al. (1965). Both these authors used the same method (the conversion of pyruvic acid to lactic acid) and found that the excretion in the urine of healthy non-pregnant women was more or less of the same order as that of normal pregnant women in the 3rd trimester (ca. 5 000 i.u. 8h).

On the other hand in patients with pre-eclampsia the U LDH excretion was raised (ca. 40 000 i.u. 8 h).

The purpose of the present study is to investigate the urinary protein pattern and urinary LDH-isoenzyme pattern in normal pregnancy and in pre-eclampsia using the method of disc electrophoresis.

Disc electrophoresis was first developed and described by Davis & Ornstein (1964). In disc electrophoresis, polyacrylamide gel is used as the electrophoretic medium. The most characteristic property of this technique is the possibility of varying the pore-size of the gel medium in relation to the varying size of the ions. In addition, the method includes concentration of the ion material so as to give a clear-cut band as the starting point of the true electrophoresis. The gel consists of three layers: the uppermost layer "sample gel" contains the ion material where ion-concentration is initiated. The middle layer "spacer gel" serves to complete the process of concentration whereby the proteins are simultaneously piled up according to decreasing electrical mobility such that the order of the subsequent fractioning is already present at this stage. Fractioning proceeds in the lowest layer "small-pore gel" and in this gel the pore-size can be varied. Fractioning with the use of disc electrophoresis has led to the identification of 49 protein fractions in serum.

Apart from its fractioning ability use can also be made of the method's ability to concentrate, which means that the electrophoresis can be carried out on dilute protein solutions, such as normal urine, without preceding concentration of the protein solution. A more detailed account of the method is given by Hemmingsen (1967) and Hemmingsen et al. (1968).

METHODS

All urine specimens were collected as 4 h samples. The volume was measured and examination for protein, glucose and blood was carried out using Labstix (Ames). Microscopy was carried out in all cases by examination

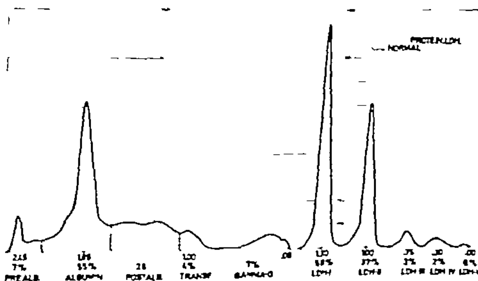


Fig. 2. Scanning diagram of protein pattern and LDH-isoenzymes after disc electrophoresis of urine from normal non-pregnant women.

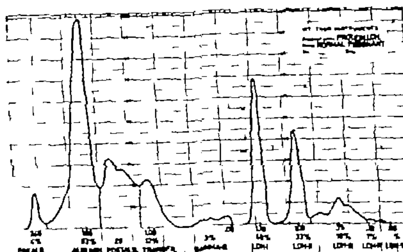


Fig. 3. Scanning diagram of protein pattern and LDH-isoenzymes after disc electrophoresis of urine from normal pregnant women.

of centrifuged deposits for erythrocytes, leucocytes, casts and bacteria.

20 ml of the total 24-hrs sample was dialysed against running water for 4 h using dialysing-tube (no. 1 109-400 Kalle AG, Wiesbaden). The dialysed unconcentrated urine was examined for total protein content by the method of Kjeldahl (1884). Urinary LDH activity was estimated by the Biochemica Test Combination UV-test®.

Protein fractionation was carried out by disc-electrophoresis. Glass tubes of 5 mm diameter and 150 mm in length were employed. The glass tubes were inserted into an electrophoretic apparatus consisting of upper and lower buffer chambers (cathode and anode respectively). The electrophoretic analysis lasted 2 hours, 2 hours for the concentration process, 30 min for the fractionation. The protein fractions were stained with Amido Schwarz and the LDH isoenzymes were developed with nitroblue-tetrazolium, as described by Goldberg (1963) (Fig. 1). The protein fractions and LDH isoenzymes were scanned in a Vitatron Universal Densitometer (see Figs. 3–4).

After the disc electrophoresis the protein fractions were identified according to their relative mobilities (R_M) using transferrin as reference ($R = 1.00$). It was decided to describe only five specific fractions even though it was possible to identify several other fractions whose presence was inconstant. The fractions were divided into groups according to their relative mobilities: prealbumin (R 1.85), albumin ($R = 1.85$), postalbumin (R 1.85, $R > 1.00$), transferrin ($R = 1.00$) and gamma-globulin (R 1.00, R 0.00). The LDH isoenzymes were likewise identified as to their relative mobilities. Five isoenzymes were described. LDH-I (R = 1.30), LDH-II (R 1.00), LDH-III (R_M 0.75), LDH-IV (R 0.30) and LDH V (R_M 0.00).

MATERIAL

The series consisted of three groups.

Group I. 24 normal, non-pregnant women.

Group II. 28 normal pregnant women.

Group III. 12 pregnant women with pre-eclampsia.

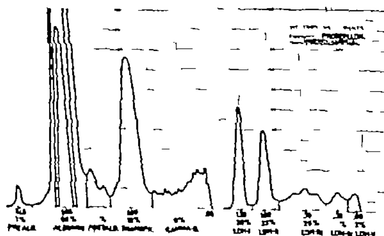


Fig. 4. Scanning diagram of protein pattern and LDH isoenzymes after disc electrophoresis of urine from patients with pre-eclampsia.

Table I *a*. *Protein fractions in 24 h urine in 24 normal non-pregnant women after disc electrophoresis*

	Pre albumin	Albumin	Post albumin	Transferrin	Gamma globulin
Percentage distribution	10 4	52.3	22.6	6.1	7 4
S.D	6.5	15 1	10.1	2.4	3.4
Protein-excretion mg/24h	11 6	64.8	25.9	6.8	8.2
S D	7.2	41.9	14.2	2.8	4.5

S.D = Standard Deviation.

Table I *b* *LDH isoenzymes in 24 h urine in 24 normal non-pregnant women after disc electrophoresis*

	LDH-I	LDH-II	LDH-III	LDH-IV	LDH-V
Percentage distribution	58 8	28.7	7.5	3.2	1.9
S.D	11 4	9 4	7 1	4.2	3.0

S.D = Standard Deviation.

All three groups fulfilled the following conditions. no previous history of urinary tract diseases or hypertension. The urine must not contain erythrocytes, leucocytes, bacteria or glucose and, in addition, for groups I and II, no protein (viz. negative Labstix®).

Group II had BP below 140/90 and no, or only insignificant, ankle swelling. Group III were selected according to Trolle s criteria (1959). iz. BP ≥ 140/90 proteinuria > ‰ and obvious oedema of the ankles, face and hands or a weight gain of more than 1 kg per week in the last trimester—two of these symptoms being required simultaneously

In groups II and III the 4 h specimens ere collected 1 3 weeks before the xpected date of delivery in all cases. All the patients in groups II and III had normal serum creatinine levels (< 1.3 mg 100 ml).

RESULTS

Group I

The average 24 h diuresis was 1 200 ml The average total protein excretion was 118 mg 24 h (S.D 47 mg/24 h) The average U LDH activity was 7 000 i.u 24 h (S.D 5 000 i.u. 24 h) The percentage distribution of the protein fractions and the average daily protein xcretion as well as the percentage distribution of the LDH isoenzymes, is shown in Table I *a* and *b*

Group II

The average 24 h diuresis was 1 100 ml The average total protein excretion was 171 mg/24 h (S.D 70.9 mg/24 h) that is a significantly greate protein excretion than in normal non-pregnan women ($p < 0.005$).

The average U LDH excretion was 9 000 i.u. 24 h (S D 6 000 i.u./24 h) which is not significant compared with normal non-pregnan women ($p = 0.30$). The percentage distribution of the protein fractions and the average daily protein excretion is shown in Table II *a*. The percentage distribution suggests smaller variation than in the normal non-pregnant group. Post albumin and transferrin fractions are raised at the expense of the albumin fraction. It can be seen from Table II *a*, that none of the described shifts was significant in comparison with the percentage distribution of the protein fractions in the normal non pregnant group. On the other hand, when the absolute values are considered it can be seen (Table II *a*) that both the transferrin and postalbumin fractions were significantly raised as compared with the normal non-pregnant group ($p < 0.001$).

The percentage distribution of the LDH iso-

Table II *a*. *Protein fractions in 24 h urine in 28 normal, pregnant women after disc electrophoresis*

	Pre albumin	Albumin	Post albumin	Transferrin	Gamma globulin
Percentage distribution	10 5	45.4	29 0	8 6	6 8
S D	8–	10.6	7.0	4 4	4 0
T-test (*P*)	> 0.1	< 0.1	< 0.02	< 0.02	> 0 1
Protein-excretion mg 24h	19 4	76.8	48 5	14 5	1 0
S D	1 7	35 4	24.2	8 7	9.2
T-test (*P*)	0 1	0.1	< 0.001	< 0.001	0 1

S.D = Standard Deviation

T-test (*p*-value) for the difference from normal, non-pregnant women.

Table II *b* *LDH-isoenzymes in 24h urine in 28 normal, pregnant women after disc electrophoresis*

	LDH I	LDH II	LDH III	LDH IV	LDH V
Percentage distribution	56 0	27 4	10.1	3 9	2.5
S.D	13 7	7 6	8 5	5 0	4–
T-test (*P*)	0 1	0 1	0 1	0 1	> 0.1

S D Standard Deviation.

T-test (*p*-value) for the difference from normal, non-pregnant women

Table III *a*. *Protein fractions in 24 h urine in 12 patients with pre-eclampsia after disc electrophoresis*

	Diuresis (ml/24 h)	Total protein (mg/24 h)	Prealbumin		Albumin		Postalbumin		Transferrin		Gammaglobulin	
			%	(mg/24 h)	%	(mg/24 h)	%	(mg/24 h)	%	(mg/24 h)	%	(mg/24 h)
1.	1 230	517	3	15	61	315	14	70	21	108	1	5
2.	1 765	561	10	56	43	242	35	196	8	45	6	34
3.	740	850	1	9	80	680	5	43	10	85	2	17
4.	1 360	503	1	5	41	208	48	242	7	35	2	10
5.	780	880	1	9	65	572	10	88	20	176	3	26
6.	530	890	1	9	78	695	4	36	15	134	1	9
7	1 275	612	0	0	76	465	6	37	16	98	2	12
8.	925	3 740	2	75	73	2 700	3	112	18	674	4	150
9	650	380	10	39	56	214	18	70	13	51	7	27
10.	700	810	0	0	72	582	6	49	20	162	2	16
11	1 260	1 770	1	18	71	1 260	9	160	16	282	2	35
12.	760	1 250	1	13	69	865	8	100	21	262	1	13
Average		1 064	2.6	20.6	65.4	739.8	13.8	100.3	13.4	176.0	2.6	29.5
S.D.		885	3.4	22.6	12.4	681.3	13.2	63.9	4.8	168.4	1.9	37.5
T-test (p)		0.01	0.005	0.1	0.001	<0.01	<0.005	<0.005	<0.005	<0.01	<0.005	>0.1

S.D. Standard Deviation.
T-test (p-value), for the difference from normal pregnant women.

enzymes is shown in Table II *b*. There were in this case only slight, non-significant variations when compared with the normal, non-pregnant group.

Group III

The average 24 h diuresis was 1 100 ml. The average protein excretion was 1 064 mg/24 h (S.D. 885 mg/24 h), which was a significant increase in relation to the normal pregnant group (p 0.01). The average U-LDH excretion was 13 000 u/24 h (S.D. 9 000 u/24 h), but this was not significant when compared with the normal pregnant group ($p > 0.2$).

The percentage distribution and daily protein excretion are shown in Table III *a*. The percentage distribution showed significant changes in all fractions. Prealbumin, postalbumin and gamma-globulin fractions were decreased, while albumin and transferrin fractions were raised. Study of the individual results showed the postalbumin and gamma-globulin fractions to be the most unstable. However in all cases, the gamma-globulin fraction was quite small.

Considering again the absolute values (Table III *a*) it can be seen that the prealbumin fraction was unchanged while the other fractions were raised, the albumin and transferrin fractions significantly so when compared with the normal pregnant group (p 0.01). The increase in the postalbumin and gamma-globulin fractions was insignificant.

The percentage distribution of the LDH isoenzymes is shown in Table III *b*. LDH-I was significantly decreased ($p < 0.005$), LDH-II unchanged while LDH III, IV and V were raised

Table III*b*. *LDH-isoenzymes in 24 h urine in 12 patients with pre-eclampsia after disc electrophoresis*

	Total LDH-activity (u/24 h)	LDH-I	LDH-II	LDH-III	LDH-IV	LDH-V
1	12 000	48	26	17	9	0
2.	14 000	22	30	22	27	0
3	3 000	0	0	0	0	0
4.	19 000	40	40	19	1	0
5	20 000	35	49	16	0	0
6	1 000	45	29	22	3	1
7	14 000	40	31	18	11	0
8	32 000	32	34	24	10	0
9	2 000	0	0	0	0	0
10	3 000	62	11	0	18	10
11	20 000	36	32	6	19	7
12.	10 000	28	28	16	10	20
Average	12 500	31.8	30.7	16.0	10.8	3.8
S.D.	8 900	10.3	9.7	7.1	8.1	6.4
T-test (p)	0.1	<0.005	0.1	0.1	<0.05	>0.1

S.D. Standard Deviation.
T-test (p-value), for the difference from normal, pregnant women.

Table IV *The contribution of the individual protein fractions to proteinuria in normal pregnancy and in pre-eclampsia in proportion to normal non-pregnant condition*

	Pre-albumin	Albumin	Post albumin	Transferrin	Gamma globulin
Normal pregnancy					
Factor	1 7	1.2	1 9	2.4	1.5
Percentage	19.5	13 8	21 8	27 6	17.[illegible]
Pre-eclampsia					
Factor	1 8	11 4	3 9	[illegible]5 9	3 6
Percentage	3.9	[illegible]4.5	8.4	55 6	7 7

in comparison with the normal pregnant group, but not significantly so

In patients No 3 and 9 the LDH isoenzyme fractionation could not be carried out, presumably due to the combination of low U LDH activity and non-dialysable LDH inhibitors.

In order to decide in which way the individual protein fractions contribute to the raised proteinuria in normal pregnancy and pre-eclampsia as compared with normal non-pregnancy the following ratio has been devised

$$\text{Factor} = \frac{\text{mg urinary protein in pats with pre-eclampsia/or normal pregnant women}}{\text{mg urinary protein in normal non pregnant women}}$$

Subsequently the percentile part of this factor in proteinuria has been calculated. The results are shown in Table IV and Fig 5 It can be seen that the biggest change in the protein pattern compared with normal non-pregnant individuals is found in the albumin and transferrin fractions (24 .5 and 55 6 respectively)

DISCUSSION

Just as in normal non-pregnant women Berggård (1961) and Hemmingsen et al (1968) normal pregnant women excrete small amounts of protein in their urine The quantity of this proteinuria has been variously reported thus Addis (1948) considers a 24 h excretion of more than 60 mg as pathological while Dieckmann (1952) states that quantitative urinary protein values in normal pregnancy vary between 0–300 mg/24 h. Nettles & Flanigan (1968) conclude that a protein excretion of 250–300 mg/24 h can usually be accepted as physiological proteinuria during pregnancy Likewise, slight proteinuria at the end of labour is regarded as physiological, Dieckmann (1952)

The 28 normal pregnant patients in the present investigation showed an average 24 h protein excretion which was significantly raised in comparison with the the excretion in the normal non-pregnant group. The percentage composition of the individual fractions was only slightly altered. Thus the albumin fraction was reduced at the expense of the postalbumin and transferrin fractions, which were raised. Prealbumin and gamma-globulin fractions remained almost unaltered. Similar comparisons between the urinary protein fractions in normal non pregnant and normal pregnant women do not seem to have been reported in the literature.

Consideration of the absolute values (Table II a), reveals that all protein fractions are increased and that the postalbumin and transferrin fractions are significantly increased in comparison with the normal non-pregnant group. The likely explanation of this could be that transferrin crosses the glomerular membrane as easily as albumin. Several authors—*Bayer (1966), Di Alvarez (1961)*, Dieckmann (1952) Mack (1955)—found the beta-globulin fraction in plasma raised in the final trimester Since the high molecular beta-lipoproteins can hardly be expected to cross the glomerular membrane it would seem that the beta-globulin

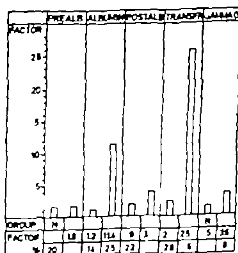


Fig 5 Diagram of the distribution of the individual protein fractions to the proteinuria in normal pregnancy and in pre-eclampsia in proportion to the normal, non-pregnant state N normal pregnancy P pre-eclampsia

fraction of 9.9% excreted in the urine of the series reported by Lorinz et al. (1961) is in fact transferrin. Reports on the molecular weight of transferrin vary between ca. 74 000 and 90 000, that is, slightly greater than the molecular weight of albumin which is ca. 70 000. In contrast, Niesert (1962) using antitransferrin serum could not show the presence of transferrin in the urine of normal pregnant women, a finding which could not be supported by the present study.

The pre-eclamptic patients of the present series all had proteinuria and the average daily protein excretion was significantly raised compared with the normal pregnant group. Compared with the percentage distribution in normal pregnancy all the protein fractions were altered (Table III *a*): prealbumin, postalbumin and gamma-globulin fractions were significantly decreased, while albumin and transferrin fractions were significantly raised. Expressed in mg protein per 24 hours (Table III) the raised protein excretion involved all the fractions except the prealbumin excretion which was almost unchanged. Both the albumin and transferrin fractions were significantly raised in relation to the normal pregnant group. It can be seen from Table IV and Fig. 5 that the albumin excretion is more than 11 times greater than in normal non-pregnant women, while the transferrin excretion is almost 6 times greater.

The marked increase in transferrin excretion is not easily explained. As was the case with normal pregnant women, the beta-globulin fraction is also reported as raised in pre-eclampsia (De Alvarez, 1964, Friedberg, 1951, Lorinz, 1961). Mack (1955) on the other had, found the beta-globulin fraction in plasma decreased. Review of the literature has not revealed any investigations into transferrin metabolism during normal pregnancy or in pre-eclampsia, but Jensen et al. (1968) found in patients with nephrotic syndrome, that transferrin synthesis was raised above the normal and that this synthesis occurred faster than that of albumin. It can only be surmised that similar conditions ... also in patients with pre-eclampsia. In any case it is striking that the excretion of transferrin is so much higher than the other fractions.

Both Parviainen et al. (1951) and Lorinz et al. (1961) discovered ... beta-globulin fraction of approximately the same order of size as the transferrin fraction found in the present investigation. However Lorinz et al. (1961) found that the relative size of the beta-globulin fraction decreased with increase in severity of the pre-eclampsia. This could not be verified by the present investigations (see Table III *a*), since the severest cases of pre-eclampsia (nos. 5–12) showed a larger percentage *transferrinuria than the whole group.*

The albumin fraction is responsible for by far the largest portion of the total proteinuria. Parviainen et al. (1951) found a relative albumin fraction of 50–60%—rising with increasing severity of pre-eclampsia, which is the closest one can find to our results. On the other hand it was not possible to confirm the results of Lorinz et al. (1961), who found an average percentage albumin fraction of 52%—falling to 36% in the most severe cases of pre-eclampsia. From Table III *a* it can be seen that in the present series the worst cases of pre-eclampsia (nos. 5–12) show a greater percentage albumin fraction than the rest of the group.

It is not surprising that albuminuria rises with severity of pre-eclampsia, when one considers that Hoeger (1968) demonstrated that the synthesis of albumin in pre-eclamptics is raised significantly in relation to that of the normal pregnant woman.

Finally neither could we support the results of Lorinz et al. (1961) and Parviainen et al. (1951) concerning the proportion of gamma-globulin in the total proteinuria. Both these authors found values 3–4 times larger than in the present series. Moreover in the severest cases, Lorinz et al. (1961) found a gamma-globulin excretion of 34%.

The excretion of U LDH in the 24 h urine of the normal pregnant group was only slightly raised, compared with that of the normal, non-pregnant group. This complies with the findings of Bauer et al. (1965) and Santoni et al. (1965). The LDH isoenzyme pattern is almost identical in normal pregnancy and in the normal non-pregnant women.

In patients with pre-eclampsia, the total LDH excretion is highly variable. The average total excretion is raised in comparison with the normal pregnant group but not significantly so. There is ... positive correlation between the quantity of proteinuria and the excretion of U LDH (= 0.64), whilst no correlation is found between U LDH excretion and severity of pre-eclampsia.

Thus, in only some cases, can we verify the

Table IV. *The contribution of the individual protein fractions to proteinuria in normal pregnancy and in pre-eclampsia in proportion to normal non-pregnant condition*

	Pre-albumin	Albumin	Post albumin	Transferrin	Gamma-globulin
Normal pregnancy					
Factor	1.7	1.2	1.9	2.4	1.5
Percentage	19.5	13.8	1.8	27.6	17.[illegible]
Pre-eclampsia					
Factor	1.8	11.4	3.9	25.9	3.6
Percentage	3.9	4.5	8.4	55.6	7.7

in comparison with the normal pregnant group, but not significantly so.

In patients No. 3 and 9 the LDH isoenzyme fractionation could not be carried out, presumably due to the combination of low U LDH activity and non-dialyzable LDH inhibitors.

In order to decide in which way the individual protein fractions contribute to the raised proteinuria in normal pregnancy and pre-eclampsia as compared with normal non-pregnancy, the following ratio has been devised.

$$\text{Factor} = \frac{\text{mg urinary protein in pats with pre-eclampsia/or normal pregnant women}}{\text{mg urinary protein in normal non-pregnant women}}$$

Subsequently the percentile part of this factor in proteinuria has been calculated. The results are shown in Table IV and Fig. 5. It can be seen that the biggest change in the protein pattern compared with normal non-pregnant individuals is found in the albumin and transferrin fractions (_4% and 55 6 respectively).

DISCUSSION

Just as in normal non-pregnant women Berggård (1961) and Hemmingsen et al. (1968), normal pregnant women excrete small amounts of protein in their urine. The quantity of this proteinuria has been variously reported, thus Addis (1948) considers a 24 h excretion of more than 60 mg as pathological, while Dieckmann (195_) states that quantitative urinary protein values in normal pregnancy vary between 0–300 mg _4 h. Nettles & Flanigan (1968) conclude that a protein excretion of 250–300 mg/24 h can usually be accepted as physiological proteinuria during pregnancy. Likewise, slight proteinuria at the end of labour is regarded as physiological. Dieckmann (1952).

The 28 normal pregnant patients in the present investigation showed an average 24 h protein excretion which was significantly raised in comparison with the the excretion in the normal non-pregnant group. The percentage composition of the individual fractions was only slightly altered. Thus the albumin fraction was reduced at the expense of the postalbumin and transferrin fractions, which were raised. Prealbumin and gamma-globulin fractions remained almost unaltered. Similar comparisons between the urinary protein fractions in normal non-pregnant and normal pregnant women do not seem to have been reported in the literature.

Consideration of the absolute values (Table II a), reveals that all protein fractions are increased and that the postalbumin and transferrin fractions are significantly increased in comparison with the normal non-pregnant group. The likely explanation of this could be that transferrin crosses the glomerular membrane as easily as albumin. Several authors—Bayer (1966), D. Alvarez (1961), Dieckmann (195_), Mack (1955)—found the beta-globulin fraction in plasma raised in the final trimester. Since the high molecular beta-lipoproteins can hardly be expected to cross the glomerular membrane it would seem that the beta-globulin

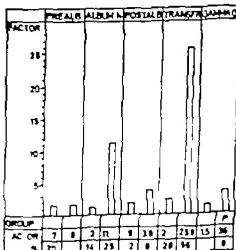


Fig. 5. Diagram of the contribution of the individual protein fractions to the proteinuria in normal pregnancy and in pre-eclampsia in proportion to the normal non-pregnant state. N: normal pregnancy. P: pre-eclampsia.

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A DYSPLASTIC GIRL WITH AN INHERITED PARTIAL C TRISOMY

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Abstract. A dysplastic girl with partial C trisomy is described. Signs met with in other chromosome syndromes are also discussed. The partial C trisomy is caused by familial C/C translocation. The mother of the proposita had five spontaneous abortions.

A balanced reciprocal translocation means the exchange of chromosome segments between two *different* chromosomes without loss or gain of chromosome substance. Translocations of this type are found in 0.3% of a normal population (1). Among families (couples) with repeated or habitual abortions, the translocation frequency is somewhat higher. Thus, in more than 150 families (300 parents) studied, three women with balanced translocations were found (8, 11). On the other hand, when one of the parents has a balanced translocation, the frequency of spontaneous abortions has been found to just exceed 20% (4). This is little above the level in the general population, estimated to be about 15%. The relation between translocations and spontaneous abortions is interesting and still not completely understood. Punnett (9) found a higher risk of spontaneous abortions, 30–40%, when one of the parents is a balanced translocation carrier.

In the present paper a brief report is given of a family with many abortions and a chromosomal translocation.

CASE REPORT

The proposita, a girl 14 years of age, was admitted to the hospital because of mental retardation. The proposita was born to a 37-year-old mother and 34-year-old father following a 40 week gestation. The parents are physically and mentally normal. There was no consanguinity. One older sister and one older brother were phenotypically normal. The mother had had five spontaneous abortions (Fig. 1). Four were early during the 2nd–3rd month, and one was in the 3rd–4th month.

Previous history

The birth weight was 3 300 g and the head circumference was 33 cm. Postnatally it was noted that the proposita had a weak cry, a peculiar face and dysplastic ears. She was found to be mentally retarded by the first year of life. She could sit at the age of 1 year and began to walk at the age of 3 years. Speech development was retarded; she could only repeat simple words at the age of 8 years.

Present condition

Physical examination showed a well-nourished girl, of short stature (146 cm) and 44 kg weight. The tubera temporalia were hypoplastic, but the head was not microcephalic—circumference 52 cm and cephalic index 0.74 (Fig. 2). The external ears seemed to have a normal morphology. The corners of her mouth were always descendent. The skin was marbled. There was a pronounced thoracic kyphosis and a scoliosis. Hyperflexibility in the wrists and finger joints was noted. There was no ulnar deviation in the wrists. A four-finger line was found in the left hand (Fig. 3). The fingers were long and tapering and the nails were dysplastic on some fingers (Fig. 4). Pronounced clinodactyly was noted. The feet were somewhat dysplastic. The nails were missing on two toes and were hypoplastic on the others. There was no cardiac murmur.

She was a neat and tidy girl and was able to say some three-word sentences.

Radiological studies

An X-ray of the heart and the chest was normal. The pelvis was abnormal with a smaller iliac ala on the right side. The right inferior pubic ramus was not completely developed. Urography showed a double renal pelvis and double ureter on the right side.

Laboratory studies

The activity of the enzyme galactose-1-phosphate uridyl transferase was raised, 44.0 units/g Hb. The value found

report made by Santoni et al. (1965) that patients with pre-eclampsia show raised U-LDH excretion (see Table III *b*).

The LDH isoenzyme pattern is clearly divergent from the normal pregnancy pattern. From Table III *b* it can be seen that LDH I is significantly decreased in comparison with the normal pregnant group. In addition taking consideration of individual results, one finds an overall reduction of LDH I and/or an increase in LDH III, IV and V completely independent of the total activity. LDH II is more or less unaltered. Thus relatively more of the slow-migrating electrophoretic isoenzymes are excreted in pre-eclamptics whilst the fastest migrating ones dominate the picture in normal pregnancy and the normal non-pregnant group.

It has been reported in the literature that LDH I and LDH II are found in tissue where the oxygen tension is high (Dawson et al., 1964). In the renal cortex, which has a high oxygen tension, the fastest moving isoenzymes are dominant (LDH V is not found) whilst the slowest moving iso-enzymes are dominant in the renal papillae where oxygen tension is low (Fine et al. 1963, Aukland & Krogh, 1960, Kean et al., 1964, Richterrich et al. 1961). Güttler et al. (1963 and 1965) showed that urine collected from the ureter of an ischaemic kidney had a markedly higher LDH V activity than that of urine from the ureter of the same patient's other (non-ischaemic) kidney.

Similarly we consider that the relative shift of the LDH-isoenzyme pattern from the fast moving towards the slow moving in patients with pre-eclampsia can be explained by lowered oxygen tension in the kidney tissue due to arterial contraction which has been reported by Altcheck (1968) amongst others. Moreover the LDH isoenzymes released from damaged renal tissue must contribute to a certain extent, to U-LDH excretion, even though the fact that the U-LDH excretion in several severe cases of pre-eclampsia being normal or even lowered seems to contradict this.

REFERENCES

Addis, T. Glomerular nephritis, diagnosis and treatment. Macmillan, New York, 1948.

Altcheck, A., Albright, N. L. & Sommers, S. C. Obstet Gynec 31 595 1968.

Arnborst, V. Arch Gynäk 204 147 1967.

Aukland, N. & Krogh, J. Nature 185 671 1960.

Baker N. & Rowan, T. Amer J Med Techn 31 262, 1965.

Bayer H., Z Geburtsh Gynäk 165 134 1966.

Berggård, J. Arch Kem 18 291, 1961.

Davis, B. J. Ann N Y Acad Sci 121 404, 1964.

Dawson, D. M. Goodfriend, T. L. & Kaplan, N. D. Science 143 929 1964.

De Alvarez, R. R., Afonso J. F. & Sherrard, D. J. Amer J Obstet Gynec 8? 1096, 1961.

De Alvarez, R. R. & Afonso, J. F. Amer J Obstet Gynec 88 774 1964.

Dieckmann, W. J. The toxemias of pregnancy 2nd edn. C. V. Mosby Co., St. Louis, 195-.

Fine, I. H. Kaplan, N. O. & Kuftinec, D. Biochemistry 2 116, 1963.

Friedberg, V. Deutsch Med Wschr 76 793, 1951.

— Zbl Gynäk 80 1930, 1968.

Geyer H., Klin Wschr 46 446, 1968.

Goldberg, E. C., Science 139 602, 1963.

Güttler F. Clausen, J. Pedersen, A. & Schiøler M. Ugeskr Læg 125 1551 1963.

Güttler F. & Clausen, J. Enzymol Biol Clin 5 5- 196-.

Hemmingsen, L. Ugeskr Læg 32 1033 1967.

Hemmingsen, L. & Skov F. Clin Chim Acta 19 81 1968.

Höneger P. Scand J Clin Lab Invest 2 177 1968.

Jensen, H., Bro-Jørgensen, K., Jarnum, S., Olesen, H. & Ysaling, M. Scand J Clin Lab Invest 1 793 1968.

Kean, L. E., Adams, H. P. Davies, H. C., Winters, R. W. & Davies, R. E. Biochim Biophys Acta 64 403 196-.

Kjeldahl, J. En ny metode til kvælstofbestemmelse i organiske stoffer. Meddelelse fra Carlsbergs laboratoriet II. bind, 1. hæfte 1 1883.

Konttinen, A. & Pyorälä, F. Scand J Clin Lab Invest 15 429 1963.

Lerinx, A. B., McCartney C. P. Pottinger R. E. & H. K. H., Amer J Obstet Gynec 82 -52, 1961.

Mack, H. C., The plasmaproteins in pregnancy. Charles C. Thomas, Springfield, Ill., 1955.

McEwan, H. P. J Obstet Gynaec Brit Comm 75 789 1968.

Nettles, J. B. & Flanigan, W. J. Clinical obstetrics and gynecology vol. 11 no. - Hoeber Medical Division, 1968.

Niesert, W. Klin Wschr 18 979 196-.

Ornstein, L. Ann N Y Acad Sci 1 1 3 1 1964.

Parvlainen, S. Soiva, K. & Ehrnrooth, C. A. Scand J Clin Lab Invest 3 82, 1951.

Richterrich, R. & Franz, H. E. Biochem Z 334 149 1961.

Royer P. Broyer M. & Nordmann, Y. Path Biol 15 803 1967.

Santoni, G. & Arezzi Bora, E. Ann Ostet Ginec 87 416, 1965.

Trolle, D. Nomenclatura Obstetricia. Copenhagen, 1959.

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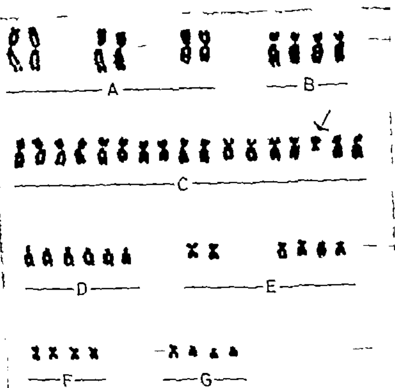


Fig. 5 Karyotype of the propositus with 47 chromosomes. The extra chromosome (arrow) is placed in the C group because of the aberration found in the mother's karyotype.



Fig. 6 Karyotype of the mother with 46 chromosomes and two translocation chromosomes (arrows), C/C translocation. For further information, see the text.

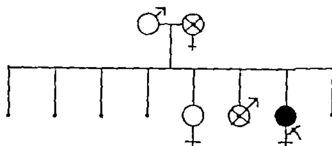


Fig 1 This pedigree shows the inheritance of the translocation. The brothers and sisters of the mother had normal chromosomes. The maternal grandparents were not alive. ○ normal karyotype; ⊗ translocation; ● abnormal phenotype, unbalanced chromosomal aberration spontaneous abortion.

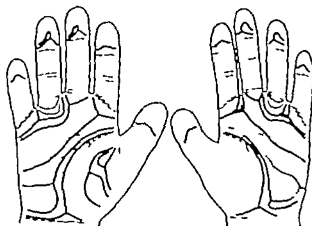


Fig 3 Notice the six arches on finger tips, and a four finger line in the palm of the left hand.

in the mother was 27.4 units/g Hb Other blood tests, including enzyme and electrolyte determinations were normal.

Dermatoglyphic studies

The dermatoglyphs on the hands of the proposita and her mother were studied. The proposita showed strikingly lower total ridge count (10) than her mother (145). The atd angle was normal. There were six arches on the finger tips (Fig. 3). Arches were present on the first and fifth finger on both hands, a finding which is uncommon in normal individuals.

Cytogenetic studies

The chromosomes of the proposita, her parents, siblings, and maternal sisters and brothers were studied in blood cultures. The proposita showed a modal chromosome number of 47/XX (Fig. 5). The extra chromosome was similar to a chromosome no. 16, but somewhat smaller in some cells. The other 46 chromosomes had normal morphology.

The mother had 46 chromosomes. An abnormal karyotype was, however, consistently present (Fig. 6). Two chromosomes of the C group were abnormal. One of them was similar to the extra chromosome in the karyotype of the proposita and the other had a long arm, which was longer than any of the C group chromosomes. On the basis of the morphology of the short arms, the abnormal chromosomes were placed hypothetically as chromosomes 9 and 11. The phenotypically normal boy had the same abnormal karyotype, 46/XY. The karyotype of the father, the sister of the proposita, as well as the brothers and sisters of the mother were normal (Fig. 1). The maternal grandparents are deceased. Sex chromatin of the proposita and her mother were normal.

The dermatoglyphic studies were performed by Dr J. M. Berg at the Kennedy-Galton Centre, Harperbury Hospital, Hertfordshire England. Mr D. J. Lee did the drawing.



Fig Profile photograph of the proposita.



Fig 4 The left hand of the proposita demonstrating the nail dysplasia.

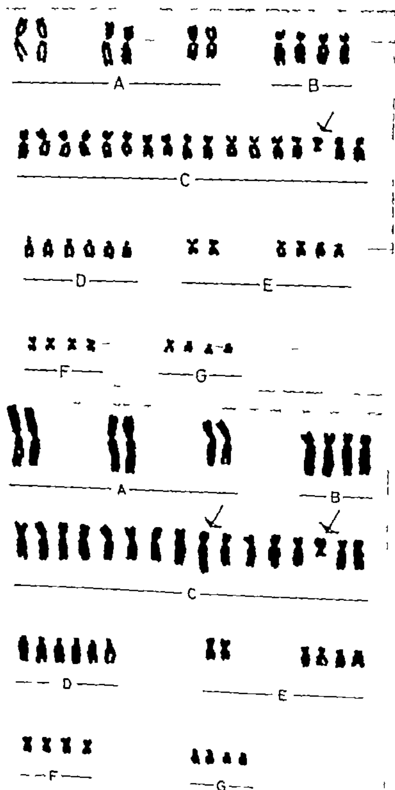


Fig 5 Karyotype of the [illegible] patient with 47 chromosomes [illegible]. The extra chromosome [illegible] (arrow) is placed in the [illegible] group because of the aberration found in the mother's karyotype.

Fig [illegible] Karyotype of the mother with 46 chromosomes and two translocation chromosomes (arrows), C C translocation For further information [illegible]

DISCUSSION

Considering the fact that the mother and her son are phenotypically normal the simplest explanation of the finding presented above is a reciprocal interchange of unequal portions of arms between two group-C chromosomes. A portion of the long arm of a group-C chromosome has become attached to another group-C chromosome. According *to this interpretation the karyotype of the* mother and her son are balanced, whereas the proposita has a partial C trisomy

A considerable overlapping of signs is found between different chromosome syndromes (3 6 10), and this patient is no exception to this rule Nail dysplasia, which is so pronounced in the present patient is for example, also found in mongoloids. They have hyperconvex nails in early infancy (5) A high galactose-L phosphate uridyl transferase activity is also present in other chromosome syndromes. The highest values are found in mongolism (2) Six arches on the finger tips are seen most often in trisomy E but are not *entirely unusual in partial C trisomies (7)* The phenotype of this patient is, however not identical to the phenotype of other partial C trisomies.

The many abortions in this family is an interesting trait and in agreement with the findings of Punnett Theoretically spontaneous abortions should be more frequent than normal

REFERENCES

1 Court-Brown, W M. & Smith, P G Human population cytogenetics. Brit Med Bull *25* 74 1969
2 Dahlqvist, A., Hall, B & Källén, B. Blood cell galactose-L-phosphate uridyl transferase activity in dysplastic patients, with and without chromosomal aberrations. Human Heredity *19* 628 1969
3 Edwards, J H Fr ccaro M Davies, P & Young R. B.. Structural heterozygosis in man Analysis of two families. Ann Hum Genet, London *26* 163 1962.
4 Ford, C. E. & Clegg, H M. Reciprocal translocations. Brit Med Bull *5* 110, 1969
5 Hall, B.. Somatic deviations in newborn and older mongoloid children f llow-up investigation. Acta Paediat Scand *59* 199 1970
6. Hall, B.. Del yed ontogenesis *in human trisomy* syndromes. Hereditas *52* 334 1965
7 Hall, B & S emmingsen, N An inherited B C translocation in a dysplastic girl w th partial C trisomy Acta Paediat Scand *58* 181 1969
8 Polani, P E.. Autosomal imbalance and its syndromes, ncluding Dow s. Brit Med Bull *25* 81 1969
9 Punnett, H. H Personal communication.
10. Rohde, R. A. & Catz, B.. Maternal transmission of a new group-C (6/9) chromosomal syndrome. Lancet *17* 838 1964
11 Wilson, J A. A prospective cytogenetic study of recurrent abortion. J Med Genet 6 5 1969

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MALIGNANCY DURING PREGNANCY

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Abstract The incidence of malignant tumours of different types during pregnancy was studied. Special attention was paid to the presence and treatment of preinvasive and invasive carcinoma of the cervix uteri. The series consisted of 100 malignancies of different types in pregnant patients treated at Departments I and II of Obstetrics and Gynaecology University Central Hospital, Helsinki, during 1950–69 The total number of pregnant patients admitted during this period was 153 424 and the incidence was thus 0 07% In 65 cases interruption of pregnancy was the sole intervention as the patient had been or was treated elsewhere. Of these cases, 63 were extragenital malignancies and two were carcinoma in situ of the cervix. The material included another 13 cases of carcinoma in situ of the cervix, making an over-all incidence of 0 009%. Invasive carcinoma of the cervix was diagnosed in 17 patients They were all treated at this clinic The incidence was 0 01% Over 5 years have elapsed from the treatment of 9 patients. Eight of these 9 patients were alive after 5 years, but one died after 7 years. The patients treated less than 5 years ago are alive and asymptomatic In addition, four other malignant tumours of the genital tract and one mediastinal neoplasm that had metastasized into the abdominal cavity were diagnosed

It is generally believed that pregnancy does not cause malignant disease, with the exception of choriocarcinoma Indeed it has been shown in large series that mammary carcinoma is more common in nulliparous than in parous women. It is also more frequent in women who did not suckle their infants after delivery than those who did Some other hypothetical connections between pregnancy and malignancy have also been suggested, but without conclusive evidence.

A pregnancy and malignant disease is a fairly unusual combination, the personal experience of every clinician is inevitably limited. The only possibility in deciding on the therapy and assessing the prognosis is to resort to the literature which contains collected material from large clinics in various parts of the world.

However there are some malignant tumours such as mammary carcinoma and carcinoma of the cervix uteri which occur with sufficient frequency to permit comparisons of some kind over long period of time.

MATERIAL

The material was collected from Departments I and II of Obstetrics and Gynaecology University Central Hospital, Helsinki, from the years 1950–69 The number of pregnant patients treated at our clinics during these years was 153 424 and the number of deliveries was 137 591.

Malignant disease during pregnancy or the puerperium was established in 100 patients during the years in question, giving an incidence of 0 07% of all pregnant women (153 474). Choriocarcinomas are not included in this material.

Interruption of pregnancy was the sole procedure in 65 cases of malignancy The disease had been treated elsewhere. Only 2 of these cases involved malignancy (carcinoma in situ) in the genital area. These 63 cases are presented in Table I

As the number of cases of each disease was small in spite of the long follow-up period and as the disease was treated elsewhere we have not assessed the prognosis of the patients in this group Figures reported in the literature are presented in the discussion. They are the combined totals from several clinics.

The malignant tumour was localized in the genital area in 33 cases. With one exception these patients were treated in our clinics and it was thus possible to follow their progress. Thirteen of these cases were carcinoma in situ of the cervix and these are presented in greater detail in Table II

In 17 cases an invasive carcinoma of the cervix uteri was established during pregnancy or puerperium. (Table III)

Table IV gives the patients whose malignant tumour originated elsewhere in the genital tract. The table

Table I *Patients with interruption of pregnancy all were treated elsewhere*

Carcinoma of the breast	23
Sarcoma	10
Carcinoma of the thyroid	9
Melanoma	5
Lymphogranulomatosis	4
Leukemia	3
Carcinoma of the larynx	2
Carcinoma of the stomach	2
Carcinoma of the oesophagus	1
Carcinoma of the kidney	1
Carcinoma of the tongue	1
Carcinoma of the maxillary sinus	1
Carcinoma of the lung	1
Carcinoma in situ of the cervix	2
Total	65

also includes a case in which an ovarian tumour was first suspected but the final diagnosis was extragenital malignancy

DISCUSSION

The frequency of mammary carcinoma in the material collected by White & White (1956) from the world literature was 1 per 3 200 pregnancies. One-half were actually noted during pregnancy the remainder during lactation. In our series the frequency of mammary carcinoma was 1 per 6 670 pregnancies, and all of them were diagnosed during pregnancy It is noteworthy that the highest pregnancy rate falls in the third decade when the incidence of mammary carcinoma is lower Carcinoma of the breast runs a rapidly progressive course in association with pregnancy or lactation (Westerberg, 1946) The most optimistic overall 5 year survival rate for carcinoma of the breast occurring during pregnancy or lactation is only 13% The corresponding rate for non-pregnant women is 40–50% (Greenspan & Lesnick, 1965) Interruption of pregnancy is therefore always imperative if it is still possible to treat the mother

The incidence of carcinoma of the breast was somewhat higher in the present series than that of carcinoma of the uterine cervix (23 17). According to the Finnish Cancer Registry the total of mammary carcinomas diagnosed in all Finland in 1963 was 818 and that of carcinomas of the cervix uteri 493

Pack & Ariel (1957) stated that such connec

Table II *Cases of carcinoma in situ of the cervix uteri*

No	Year	Age	Month of pregn.	Treatment	Histology before op.	Histology after op	Survival
1	1954	33	V	Hysterect with rem. of both adnexa + X-ray	Carcinoma in situ	Carcinoma in situ	Symptomless
2	1957	30	VII	Amput port. (m. VI) + Sectio (m VIII) + X-ray	Carcinoma in situ	Carcinoma in situ	Symptomless
3	1958	38	III	Abort. spont. Amput. port.	Carcinoma in situ	Carcinoma situ	Symptomless
4	1959	44	III	Evac. et abr + Hysterect. with rem. of both adnexa	Carcinoma in situ	Carcinoma in situ	Symptomless
5	1963	40	III	Hysterectomy	Carcinoma in situ	Carcinoma in situ	Symptomless
6	1964	37	IV	Hysterectomy	Carcinoma in situ	Microcarcinoma	Symptomless
7	1965	4	Tubal pregn.	Rem. of right adn. + Cerv abr + Amput. port.	Carcinoma situ	Carcinoma situ	Symptomless
8	1967	46	IV	Hysterectomy	Carcinoma in situ	Carcinoma in situ	Symptomless
9	1968	36	II	Evac et abr + Hysterectomy	Carcinoma in situ	Carcinoma in situ	Symptomless
10	1968	41	IV	Sectio minor + Hysterectomy	Carcinoma situ	Carcinoma in situ	Symptomless
11	1968	4	III	Hysterectomy	Carcinoma in situ	Carcinoma in situ	Symptomless
1	1969	30	VI	Amput. port. + Conus. Hysterectomy	Carcinoma in situ	Carcinoma in situ	Symptomless
13	1969	5	Puerp	Amput. port + Conus Hysterect. with rem. of both adnexa	Carcinoma in situ	Carcinoma situ	Symptomless

Table III. *Cases of carcinoma of the cervix uteri*

No.	Year	Age	Month of pregn.	Stage	Treatment	Survival
1	1950	31	II	IIb	Werth. lymphadenect.+ X-ray	Death after 2 years
2	1951	29	V	Ib	Hysterect. with rem. of both adnexa + X-ray	Alive
3	1953	31	III	Ib	Werth. lymphadenect.+ X-ray	Alive
4	1954	35	V	I	Hysterect. with rem. of both adnexa + X-ray	Alive
5	1957	22	II	IIb	3 Ra + X-ray	Alive
6	1960	36	III	Ib	Werth. + lymphadenect.+ X-ray	Alive
7	1961	30	III	Ib	Werth. lymphadenect.+ X-ray	Alive
8	1961	31	III	Ib	Werth. lymphadenect.+ X-ray	Death after 7 years
9	1964	29	III	Ib	Werth. lymphadenectomy	Alive
10	1965	30	III	Ib	Werth. lymphadenect.+ X-ray	Alive
11	1965	32	IV	Ib (IV)	Werth. lymphadenect. X-ray	Alive
12	1966	36	IV	Ib	Sectio minor steril. 3 Ra. X-ray	Alive
13	1966	38	IV	I	Hysterect. with rem. of both adnexa X-ray	Alive
14	1966	29	III	I	Werth. + lymphadenectomy	Alive
15	1967	44	VI	I	Sectio minor Werth. + lymphadenect. X-ray	Alive
16	1968	26	III	Ib	Werth. lymphadenect.+ X-ray	Alive
17	1969	34	X	II	Amput. port. Sectio Werth. lymphadenect. X-ray	Alive

tive tissue tumours as neurofibromas, haemangiomas, Kaposi's sarcoma and other vascular tumours show increased incidence and striking acceleration of growth during pregnancy. As structurally there are several types of sarcoma, their location varies and relatively few sarcomas have been encountered during pregnancy, prognosis is difficult. Because sarcomas are generally highly malignant the main attention in therapy must be paid to the mother.

It is generally true that malignant growths are more common in organs which are the site of cyclic or rhythmic changes or under the control of varying hormonal influences. The thyroid gland fits the latter category. According to Friedman (1965), treatment of carcinoma of the thyroid

Table IV. *Cases with malignancy in different organs*

No.	Year	Age	Month of pregn.	Diagnosis	Treatment	Survival
1	1950	21	V	Carcinoma of the ovary Stage IIb	Werth. lymphadenect. X-ray	Death after 6 months
2	1952	25	IV	Sarcoma of the ovary	Hysterect. with rem. of both adn.	Death after 7 months
[illegible]	1953	[illegible]	VI	[illegible]	Nil	Death after 5 months
4	1957	42	III	Carcinoma of the breast with ov. metast. — [illegible] radical mastect.	Supravaginal amput. with rem. of both adnexa	Alive
5	1968	34	IV	Parovaginal Schwannoma	Exstirp.	Alive

during pregnancy depends on many factors which must decide the attitude to continuance of pregnancy Interruption of pregnancy is not indicated in all cases.

In a summary of over 1 000 cases of melanoma (Pack & Scharnagel 1951) 12 patients were pregnant when seen, and only 32 cases of malignant melanoma were associated in any way with pregnancy or lactation. Recently the 5 year survival rate in cases of malignant melanoma was reported to be the same in pregnant and nonpregnant women. Indeed women generally demonstrated a better prognosis than men (George et al. 1960) Transplacental transmission was not found among 77 pregnant females although the placenta was involved with metastatic lesions in two cases (White 1959) but in the world literature there have been 24 reported cases of maternal cancer metastasizing to the products of conception (melanoma 11 breast 4 stomach 2, lung 2 and one case each of lymphosarcoma, sarcoma, adrenal carcinoma, ethmoid and ovary) (Potter & Schoeneman 1970)

Although Hodgkin's disease, lymphomas, and leukemias may occur in pregnant women, there is no evidence that pregnancy predisposes to their development (Hoster et al 1948). Interruption of pregnancy must be decided individually

Isolated malignancies regarded even in the literature as rare during pregnancy occurred in our series. The prognosis is consequently difficult *to assess and each case must be decided in*dividually

Carter's (1957) group surveyed 8 000 obstetric patients during pregnancy or the puerperium and found that the incidence of carcinoma in situ of the cervix was 0.55% In our series, carcinoma in situ was encountered in only 0 009% of the cases. The main reason for the great difference was probably that the disease was detected in our cases incidentally without a systematic examination.

A résumé of th reports of persistent preinvasive cervical carcinoma in the literature shows that about 74% of the cases of carcinoma in situ diagnosed during pregnancy persisted after termination of pregnancy (Lapid et al 1965) Judging from the literature the scheme of treatment generally appears to be that unless more advanced changes (invasive growth) are observed pregnancy is allowed to continue and delivery may proceed normally A new examination is performed after pregnancy In addition to the examination findings, the therapy depends on the patient's age and parity

Our patients were treated more radically Pregnancy was interrupted and total hysterectomy was performed in 7 cases. In one case total hysterectomy was carried out after spontaneous abortion. In only 2 cases in which pregnancy was already more advanced (VI and VII month) was the pregnancy allowed to continue after amputation of the cervix. Total hysterectomy was performed after delivery The treatment was administered during the puerperium in 1 case and another case was associated with an extrauterine pregnancy The therapy was conservative. Microscopic examination of the surgical specimens revealed invasive growth in only 1 case.

As the progress of preinvasive carcinoma to invasive carcinoma is at present believed to take about 10 years, analysis of the prognosis is not indicated.

The incidence of invasive carcinoma of the cervix uteri in our series was 0 01% According to the literature the incidence during pregnancy is 0 03% (Stegmann 1963) Stegmann had collected the material of 30 authors (1 822 661 deliveries, 607 of which involved invasive carcinoma) According to Lapid et al (1965), the incidence varies in individual series in the range 1 case per 6 000–8 500 pregnancies. There are *series with a higher incidence The Finnish Cancer* Registry states the incidence of carcinoma of the cervix uteri for all women to be _1 cases per 100 000 females in Finland.

There is no definite evidence (Younge et al 1949 Gusberg, 1953) that cervical cancer either dedifferentiates or becomes more rapidly invasive under the influence of pregnancy or hormones. This is illustrated by the report of Kistner Gorbach & Smith (1956) and Kottmeier (1962) that the 5 year survival rate in cervical carcinoma treated before the middle of the last trimester was similar to that of the nonpregnant patients, but the maternal prognosis worsens materially *after* this time

Eight of the 9 patient in our series who survived for more than 5 years after treatment ar alive One *of them* died after 7 year The outcome can be considered good especially as there were two stage II cases. All the patients treated

r are alive and asymptomatic as regards car ›ma. The prognosis in this series is about same as that of Vara (1949) series of 18 lents with carcinoma of the cervix during the iod 1924–47 which was collected from the ne clinic.

According to the literature, the treatment of rasive cervical carcinoma is generally radical in phases of pregnancy (McKelway 1963 rombly 1963 Hunt & Symmonds, 1963 Gor n, 1965). Pregnancy is interrupted by classic aesarean section as soon as the diagnosis is ade.

Although one of the obvious reasons for surgi al removal of any neoplasm is the possibility of malignancy the occurrence of ovarian malig nancy during pregnancy is rare. Only 2–3% of ovarian tumours found during pregnancy have proved to be mal gnant (Andrews et al 1940). The rarity of this combination is confirmed by the data collected by Munnell (1963) from the literature. There were only three malignant ovarian tumours in his series. The treatment must be decided in accordance with the clinical spread of the tumour the degree of malignancy and the phase of pregnancy

Both vulvar and vaginal carcinomas are ex tremely rare during pregnancy (Collins & Barclay 1963) Not single case of this type was en countered in our series.

REFERENCES

Andrews, C J Nichols, R B & Nichols, A G Amer J Obstet Gynec 39 453 1940.

Carter B M (Dise of Greene, R R & Peckham, B M) Trans Amer Obstet Gynec 68 101 1957

Collins, C G & Barclay D L. Clin Obstet Gynec 6. 927 1963

…nish Cancer Registry Cancer Incidence in Finland, VIII, 1963

…riedman, E W I Medical, Surgical and Gynecologic Complications of Pregnancy edn. 2, p. 290. Williams & Wilkins, Baltimore, 1965

…eorge, P A Fortner V G & Pack, G T Cancer 13 854, 1960

…arton, G Acta Obstet Gynec Scand 44 71 196

…reenspan, I M & Lessick, G J I Medical, Surgi cal and Gynecologic Complications of Pregnancy edn. 2, p 790 Williams & Wilkins, Baltimore, 1965

Gusberg, S B Amer J Obstet Gynec 65 1073, 1953.

Hoster, H Dratman, M Craver F & Rolnick, H Cancer Res 8 1 1948

Hunt, A B & Symmonds, R E Clin Obstet Gynec 6 949 1963

Kottmeier H. L.: Acta Obstet Gynec Scand 41 1 1962.

Kistner R. W Gorbach, A. C. & Smith, C. V.: Obstet Gynec (NY) 9 554, 1957

Lapid, L. S., Davids, A. M. & Gusberg, S. B.: I Medical, Surgical and Gynecologic Complications of Pregnancy edn. 2, p. 349 Williams & Wilkins, Baltimore, 1965

McKelway W P Clin Obstet Gynec 6 945 1963.

Munnell, E. W Clin Obstet Gynec 6 983, 1963.

Pack, G. T and Ariel, I. M., Paul B. Hoeber, Inc., New York, 1957

Pack, G. T & Scharnagel, L., Cancer 4 374 1951

Potter J F & Schoeneman, M., Cancer 25 380, 1970.

Stegmann, H. Med Klin 58 1605 1963.

Twombly G H., Clin Obstet Gynec 6, 949 1963

Vara, P Ann Chir Gynaec Fenn 38. Suppl. 3 1949

Westerberg, S. V Acta Obstet Gynec Scand 25 Suppl. 4 1946.

White, T T & White, W C. Ann Surg 144 384, 1956.

White, L. P New Engl J Med 260 787 1959.

Younge, P A Hertig, A. T & Armstrong, D Amer J Obstet Gynec 58 867 1949

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RESULTS OF THE TREATMENT OF CARCINOMA OF THE CERVIX UTERI

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Abstract. A series of 640 cases of carcinoma of the cervix uteri collected in 1959–63 from the First and Second Departments of Obstetrics and Gynaecology University Central Hospital, Helsinki, was analysed.

The treatment for 461 (73%) of the patients was radiologic. Their 5 year cure rate was 39.1%. Combined therapy (surgery radiation) was the treatment for 173 (27%) patients and the 5 year cure rate was 82.1%. The total 5 year cure rate was 50.1%.

The 5 year cure rate for stage I (226 patients) was 81.4%, for stage II (243 patients) 44.9%, for stage III 148 patients) 16.9%, and for stage IV (17 patients) 9%. The series included 6 patients with carcinoma of the cervix and corpus of whom one was alive after 5 years.

Therapeutic results in the management of carcinoma of the cervix uteri have been reported from the First and Second Departments of Obstetrics and Gynaecology University Central Hospital, Helsinki, since 1926. The first statistics, for 1926–30, were reported by Chydenius (1936). The therapeutic results for 1931–40 were presented by Turtola (1947) and for 1941–52 by Pulkkinen and Turtola (1958). The most recent statistics are from the years 1953–58 and were compiled by Turunen & Vara (1964). The present international staging of carcinoma of the uterine cervix has been in use since about 1938. However it does not differ in principle from the earlier stage grouping which was employed by Chydenius and the results are consequently comparable in this respect.

MATERIAL

A total of 640 cases of invasive carcinoma of the cervix uteri was treated at the First and Second Departments of Obstetrics and Gynaecology University Central Hospital, Helsinki in 1959–63. In the same period 2 266 invasive uterine cervix carcinomas were diagnosed in Finland as a whole. Hence, 28.2% of the cases were treated in our clinics.

The material collected from our clinics since 1926 is presented in Table 1, which shows the size of the series and the percentage distribution by stages. The present series includes 6 cases of carcinoma of the corpus et cervix which do not appear in the table and were not classified by clinical stages.

The various series covered periods of different lengths, but the average number of patients treated per annum was: Chydenius, about 45; Turtola, about 95; Pulkkinen & Turtola, about 90; Turunen & Vara, about 123; Nieminen & Pöllänen, about 130.

TREATMENT

Combined therapy, i.e. radiation + surgery, was used chiefly for carcinomas of stages Ia and Ib and, partly for stages IIa and IIb. The patients were given a single radium treatment (radium plaque + cobalt tube), so-called preoperative radium therapy 2 weeks before the operation (Wertheim operation with lymphadenectomy). The average total dosage of radium (cobalt) was about 2 000–2 500 mg eq hours, of which the vaginal dose was approx. 1 200–1 600 mg/eq/hours and the cervical dose about 750–1 000 mg/eq/hours. External radiotherapy with X-rays (Müller' convergent moving apparatus) was begun 4 weeks postoperatively. For stage I cases the deep dose to each parametrium was 3 000–4 000 R and for stage II was 4 000–4 500 R.

The principal therapy in cases of stages II and III was radiologic. Radium (Co⁶⁰) treatment was given three times at fortnightly intervals and X-irradiation was begun immediately after the third treatment. The average total dosage of radium (cobalt) was about 8 000 mg eq hours, of which the vaginal dose was about 3 000 mg/eq/hours. The deep dose to each parametrium was 4 000–4 500 R. (The modified Stockholm method, Unoëus et al. 1960).

In stage IV and cases with carcinoma of the cervix and corpus the therapy was always radiologic. The modes of treatment mentioned above had to be varied in some

Table IV *Five-year cure rate for stages III and IV. In addition, 5 year cure rate for the carcinoma of the corpus and of the cervix group*

Therapy	Stage III		Stage IV		Corpus and cervix	
	Cases	5 year cure rate	Cases	5 year cure rate	Cases	5 year cure rate
Irradiation (combin.)	148	16.9	17	5.9	6	16.7

The 5 year cure rate for stage III was 16.9% and for stage IV 5.9%. For the corpus and cervix group it was 16.7%.

Of the total of 640 patients, 321 were alive after 5 years and the 5 year cure rate for the total series was thus 50.2%. If the 28 cases in which treatment was interrupted are disregarded, the 5 year survival rate for the total series was 52.5%.

Fig. 1 gives the survival curves for all stages of carcinoma except the group with carcinoma of the corpus and cervix.

COMPLICATIONS OF TREATMENT

Fistulae of various types developed in stages I–III in a total of 61 cases (9.5%). Seventeen of these patients had been treated by surgery + radiation and 44 radiologically. The incidence of fistulae in the former therapeutic group was 9.8 and in the latter 9.5%. The figure includes all the cases, also those in which a fistula was established in the terminal stage. Later examination of the fistulas shows how many of them were due to therapy and how many were caused directly by the carcinoma. For instance, Kottmeier (1954) deducted from his material fistulae that were diagnosed in the terminal stage which had originated after operative intervention. Table V gives the frequency of fistulae of various types.

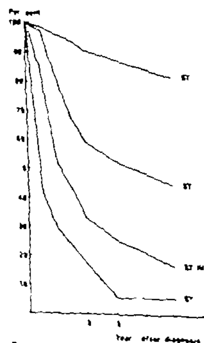


Fig. 1. Survival curves of stages I–IV.

Complaints of various kinds of urinary distress were made at the follow-up examination by 61.9% of the patients. Roentgenologic changes in the urinary tract were seen in 39.9% of the patients treated by surgery and radiation and in 20.6% of those given radiotherapy alone (hydroureter, hydronephrosis, urethral stricture, etc.).

Various intestinal complaints were reported by a total of 30.2% of the patients; 19.1% of them had been treated by surgery and radiation and 34.3% radiologically.

DISCUSSION

The annual number of patients in our clinics has increased. The average was about 45 in City

Table V *Fistulae arising as complications of therapy*

Type of Fistula	Radiation Surgery	Radiation	Total
Ureterovaginal	11	2	13
Vesicovaginal		14	16
Rectovaginal	1	23	4
Vesico- and rectovaginal	1	5	6
Colon-vaginal	2	—	2
	17	44	61

Table I. *Carcinoma of the cervix series collected from the First and Second Departments of Obstetrics and Gynaecology University Central Hospital Helsinki*

	Total Cases	Stage I ( )	Stage II ( )	Stage III (%)	Stage IV (%)
Chydenius, 1926–30	226	3 1	14 0	28.9	54.0
Turtola 1931–40	953	13..	.7 4	38 4	1.0
Putkinen & Turtola, 1941 52	1 072	7 0	41 0	76.6	5 4
Turunen & Vara, 1953–58	741	6.7	44 7	26 0	.6
Nieminen & Pöllänen, 1959–63	640*	35.3	38.0	.3.1	.7

Including 6 cases of carcinoma of the corpus and of the cervix.

Table II *Five-year cure rate for stage I*

	Stage I *a*		Stage I *b*		Total	
Therapy	Cases *n*	5 year cure rate	Cases *n*	5 year cure rate	Cases *n*	5 year cure rate
Surgery	9	100.0	—	—	9	100 0
Combin. (S+I)	23	91.3	114	86 8	137	87 6
Irradiation	3	100.0	77	68 8	80	70 0
Total	35	94.3	191	79 6	226	81 4

cases because of the patient's age, poor condition or some other reason. The cases in which the treatment had to be interrupted were included in the series (St. II = 6, St. III = 13 and St. IV = 9).

RESULTS

Table II shows the therapeutic results achieved in cases of stage I *a* and I *b* and for the stage I cases as a whole. The table also shows the distribution of the cases according to the mode of treatment. The 5 year cure rate in stage I *a* was 94 3%, in stage I *b* 79 6% and in stage I as a whole 81 4%.

Table III gives the therapeutic results for stage II as a whole and separately for stages II *a* an II *b* The 5 year cure rate was 44 9%. It wa slightly better (46 9%) for stage II *a* than II (42.6%)

173 patients with carcinoma of stage I and I were treated either by surgery alone or by surgery + radiation. Of these patients, 142 were aliv after 5 years (87 1%) The operative mortality rate was 0 6% (1 patient).

Table IV gives the results for stages III and IV in which the treatment was solely radiologic.

Cases with carcinoma of the corpus and cervix were placed in a separate group and their therapeutic results are also presented in Table IV

Table III *Five-year cure rate for stage II*

	Stage II *a*		Stage II *b*		Total	
Therapy	Cases *n*	5 year cure rate	Cases	5 year cure rate	Cases	5 year cure rate
Surgery	3	33.3	—	—	3	33 3
Combi (S I)	15	53 3	9	44 4	4	50.0
Irradiation	110	46 4	106	4..5	16	44 4
Total	128	46 9	115	4..6	43	44 9

Table IV *Five-year cure rate for stages III and IV. In addition, 5 year cure rate for the carcinoma of the corpus and of the cervix group*

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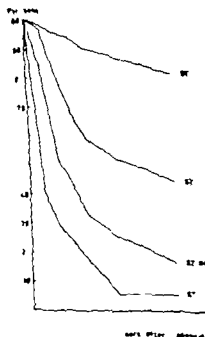


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Table VI *Five-year cure rate for the series collected from the First and Second Departments of Obstetrics and Gynaecology University Central Hospital Helsinki*

	Treated by Irradiation		Treated by Irradiation + Surgery		Total, 5 year cure rate (%)
	Cases	5 year cure rate (%)	Cases n	5 year cure rate (%)	
Chydenius, 1926–30	701	20.9	25	68.0	26 1
Turtola, 1931–40	821	23.7	110	61.8	33 7
Putkinen & Turtola, 1941–52	929	40.8	143	69.[illegible]	40 8
Turunen & Vara, 1953–58	653	44 1	88	81.8	44 1
Nieminen & Pöllänen, 1959–63	461	39 1	173	82.1	50.2

denius's material about 95 in Turtola's, about 90 in Putkinen & Turtola's, about 123 in Turunen & Vara's and around 130 in the present series. The distribution by stage (Table I) reveals a steady increase in the proportion of stage I stage II showed a continuous increase until 1953–58 but decreased significantly in the present series. The trend has been similar for stage III Stage IV accounted for over half of the total in 1926–30 today for less than 3% The change is probably due chiefly to cancer propaganda and mass examinations, and partly also to improved diagnosis (exfoliative cytology colposcopy etc.)

The prognosis of patients with carcinoma of cervix uteri has continued to improve in our clinics (Table VI) In Chydenius's series, about one fourth of the patients were alive after 5 years and in the present series, one-half (50.2%). According to the statistics compiled by Kottmeier in 1961 for the therapeutic results (radiologic therapy) for carcinoma of cervix uteri from 105 clinics in 23 different countries, the total cure rate was 43 6% However our results with radiotherapy analysed according to stage, were poorer than in Kottmeier's material It should also be noted that we have seen no improvement in this respect in the last 20 years. The greatest reason for this is the antiquated equipment employed for external therapy which has only now been retired from use (roentgen apparatus) External treatment is now given by megavoltage therapy The total cure rate in Kahanpää's material which was collected from the Radiotherapy Clinic, University Central Hospital Helsinki, was 43 8% The result is impaired by the very great proportion of late stages (stages III–IV 48.5%)

In contrast, *our operative results* (surgery + radiation) have improved steadily The 5 year cure rate in the present series was 87 1% which is of the same order as the results achieved elsewhere in the world (Christensen, 1964 Welch, 1961 Kolstad, 1968 Masterson, 1967) As the proportion of operated cases (surgery + radiation) has grown continuously in our clinics as a result of an increase in the proportion of early stages and a decrease in late stages, the improvement in the prognosis for the total material must be attributed to it. Chydenius mentioned that Wertheim's operation had been performed in our clinics to an increasing extent since 1933 Only 10 Wertheim's operations were performed in 1927–30 all of them after complete radium therapy In 1929–30 complete radium therapy was followed by a radical vaginal operation by the method of Schauta Stockel in 14 cases. Surgically treated patients in Turtola's material averaged 11 per annum, in Putkinen and Turtola's material 12, in that of Turunen and Vara 14 and in the present work 24

The incidence of fistulae in the present series was the same both for radiologically managed patients and for the patients given surgery and radiation. Overall the incidence of fistulae in different series is 10–15% of the patients treated operatively (Kjellgren 1967) The radiologically treated patients in the present series had fistulae a little more frequently than those in the cases described by Turunen & Vara (6 5 and 4 6 respectively)) The roentgenologic changes in the urinary tract are mostly reversible However it must be remembered that these changes, like catheterisation of the bladder during therapy cause

urinary tract infections which can be dangerous and even lethal for the patient, if neglected. As is only to be expected, these lesions are more frequent in the operatively managed cases.

Intestinal complaints are more common in the radiologically treated cases. This is also to be expected. It is natural that bladder and intestinal damage should arise after radiologic therapy however carefully these organs are protected. The frequency of complications reported depends primarily on how carefully the follow-up examination is performed and what changes are regarded as complications. There are comprehensive reports in the literature which mention only the occurrence of complications but not their incidence. The low figures previously reported prevent objective analysis.

REFERENCES

Cancer Incidence in Finland, Finnish Cancer Registry VII, Helsinki, 1963.

Christensen, A., Lange, P & Nielsen, E. Acta Obstet Gynec Scand 43 Suppl. 2, 59 1964.

Chydenius, J J Finska Läk. sällsk. handl. *9* 755 1936.

Kahanpää, V & Turtola, V Strahlentherapie *98* 240, 1955

Kolstad, P Personal communication, 1968

Kottmeier H.-L. Amer J Obstet Gynec *88* 854, 1964.

Masterson, J G., Clin Obstet Gynec 10 922, 1967

Pitkänen, T & Turtola, V Ann Chir Gynaec Fenn *47* Suppl. *81* 1958.

Turtola, V Acta Obstet Gynec Scand *4* 27 1947

Turunen, A. & Vara, P Acta Obstet Gynec Scand *43* Suppl. 7 62, 1964.

Unnérus, C.-E., Rekonen, A., Vuorinen, E., Turtola, V & Kivilaakso K. *43* Suppl. *1*, 1964.

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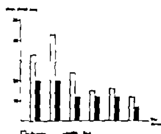
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Hematuria and so-called essential hematuria –3 tablets (1–1.5 g) –3 times daily until macroscopic hematuria is no longer present.
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Nilsson, L., Rybo G. Treatment of menorrhagia ith an antifibrinolytic agent, tranexamic acid (AMCA). A double blind investigation. Acta Obstet. Gynecol. Scand. 46 (1967) p. 5??

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Acta Obstet Gynec Scand 49: 327–330 1970

THE DIAGNOSTIC POSSIBILITIES OF A MODIFIED HYSTEROSCOPIC TECHNIQUE

Karla Edström and Ingmar Fernström

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Abstract. A modified endoscopic technique for the inspection of the uterine cavity is described. The modification consists in the injection of a clear water-soluble and viscous dextran solution into the uterine cavity through which a clear view of the latter is obtained. Thirty cases were examined by this method following hysterography. Comparative studies of the observations made at hysteroscopy and the hysterographic findings in these cases showed that hysteroscopy is of greater diagnostic value than hysterography because the nature and extent of any intrauterine lesion present can be assessed directly.

Various types of water-hysteroscopes have been used in endoscopy of the uterine cavity (Norment, 1956, Englund et al., 1957, Gribb 1960 amongst others) but the results were more or less unsatisfactory as these instruments did not afford a good view of the uterine cavity. With a view to improving the diagnostic possibilities of hysteroscopy Silander (1963) used a thin-walled and transparent latex rubber balloon which was slipped over the lens of the endoscope. The endoscope was fitted with a cannula through which the liquid which inflated the balloon was injected. The inflated balloon separated the walls of the uterine cavity and kept it sufficiently distended to make it accessible to inspection. Although Silander's technique improved the diagnostic possibilities of hysteroscopy it did not result in an entirely satisfactory view of the uterine cavity and therefore has been used only on a small scale.

The diagnostic possibilities of hysteroscopy were further developed by the use of a viscous solution instead of water. This technique as well as the observations made in the cases in which it was used, were considered to be sufficiently interesting to be reported.

CASE MATERIAL

The series of cases studied included 30 patients whose ages ranged from 22 to 56 years, the average being 32 years. All these patients had hysterography performed before hysteroscopy from 1 to 8 months previously in 7 patients and from 1 to 14 days previously in the other 23 patients.

In 25 cases the endometrial phase was determined by curettage which was done immediately after hysteroscopy and the observations made in the endoscopic examination were compared with the histological findings. In 3 of the 30 cases in this series hysterectomy was carried out within 1 month after hysteroscopy.

These 30 patients were admitted to the Department of Women's Diseases with the following diagnoses: infertility (18 cases), metrorrhagia (8 cases), habitual abortion (2 cases), oligomenorrhoea (1 case) and unexplained abdominal symptoms (1 case). In no case did a rise in temperature or any other complication occur following hysteroscopy.

HYSTEROSCOPY TECHNIQUE

The instrument consists of an endoscope, 35 cm long, fitted with a Hopkins lens which has a viewing angle 30° from its axis. The stainless steel cannula is 6 mm in diameter and is fitted with 2 two-way stopcocks. One allows introduction of rinsing solutions and the other the introduction of a thin flexible biopsy forceps. The Storz Kaltlicht Fontane (Cold Light Fountain), Universal, 150 W is used to supply light to the endoscope, the conducting cable being of glass fibres.

For endoscopic photography a miniature camera, Robot Star II is attached to the endoscope by a reflecting lens (Storz 10408 Ph), the light source being an electronic flash generator (Storz 10405 K).

Manufactured by Messrs. Karl Storz K.G., Hermannstrasse 14, 72 Tuttlingen, BRD

Under barbital anaesthesia or paracervical block the cervix is grasped on each side with a volsellum and dilated to Hegar 7. Thereafter the endoscope is introduced and the uterine cavity is washed with a few millilitres of saline solution which is injected through the cannula. 5 to 10 ml of a highly viscous dextran solution (Dextran 70 D R I[2] 35 w/v%) is then injected through the cannula. As the solution is very viscous it only flows very slowly through the Fallopian tubes into the peritoneal cavity and therefore keeps the uterine cavity distended for sufficient time to enable inspection of its whole surface. The light conduction of this dextran solution is very good and it does not become turbid so readily as does water because it is not easily miscible with blood or mucus. Haemorrhage occurred in only a few cases, usually at the end of the examination, and was so slight that it did not obscure the view.

This endoscopic technique afforded an excellent view of the uterine cavity and usually also enabled the tubal orifices to be inspected easily (Figs. 1/4). It has the advantage over Silander's technique that the endometrium is not compressed. This enables the true nature and colour of the mucosa to be assessed directly. Smaller polyps may be seen to move slightly and the vascular pattern of polyps and the structure of their mucous membrane are also clearly seen. The uterine cavity and mucosa are as clearly visualized as on macroscopic inspection of a specimen of a bisected uterus. Repeated injections of the solution result in rinsing the lens of the endoscope and the uterine cavity. The total quantity of dextran solution used in a single examination usually ranges from 50 to 100 ml. During withdrawal of the endoscope the cervical canal can be inspected.

Hysterography

The premedication of the patient consists of the injection of 1 ml of morphine/scopolamine 1 hour before examination. In no case was general or local anaesthesia induced.

Schultze's intrument without a manometer is used. Water-soluble Perjodal S[2] is injected under fluoroscopic control until uniform filling of the entire uterine cavity is obtained. Thereafter the following views are taken: a postero-anterior, a right oblique, a left oblique, a lateral and an antero-posterior. In order to maintain filling of the uterine cavity at a constant level throughout the examination about 0.5 ml of the opaque medium is injected before each exposure, the total quantity used ranging from 10 to 20 ml in a single examination.

RESULTS

In 16 cases the hysterographic findings corresponded with the observations made at endoscopy. In 4 of these cases neither examination revealed any abnormality; in 5 cases they disclosed a localized thickening of the uterine mucosa or mucosal folds, in 4 cases one or several polyps, and in the remaining 3 cases submucous fibroids were demonstrated by both examinations.

In 14 cases the hysterographic appearance did not correspond with the observations made during the endoscopic examination. These cases were divided in the following three groups (Table I).

Group I comprised 4 cases in which the changes *shown in the hysterogram* were *not seen through* the endoscope. In 2 of these there was radiographic evidence of small diverticula, the dia-

Fig. 1. Endoscopic photography of the cervix. The cervical canal does not show any abnormality. The darker area in the lower half of the picture represents the internal os.

Fig. 2. Endoscopic photograph of the uterine cavity showing the corpus region with the fundus uteri and right tubal corner. The uterine cavity does not show any abnormality. In the upper part of the picture the anterior wall of the cavity is vaguely seen.

Fig. 3. Endoscopic photograph of the uterine cavity in a menopausal woman. The fundus uteri does not show any abnormality. In the right part of the picture the left uterine wall is seen. Between the latter and the fundus is the opening into the right cornu.

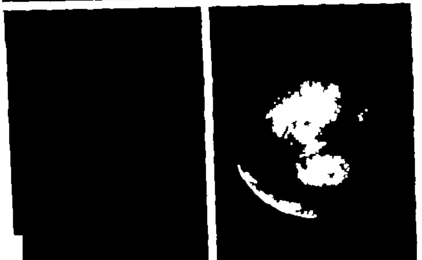
Fig. 4. Endoscopic photograph of the uterine cavity. The orifice of the left uterine tube does not show any abnormality. A drop of secretion is seen in the uterine cavity just below the tubal orifice.

Fig. 5. Endoscopic photograph of the uterine cavity. A bipartite polypus, measuring 4 mm, is seen to arise from the right anterior wall of the body of the uterus.

Fig. 6. Endoscopic close-up view of the uterine cavity. A broadbased irregularly shaped polypus, measuring mm, is seen to arise from the left posterior wall of the body of the uterus. In the lower part of the picture the endometrium is seen to be normal within small circumscribed area.

[2] Manufactured by the Pharmacia AB, Uppsala, Sweden.


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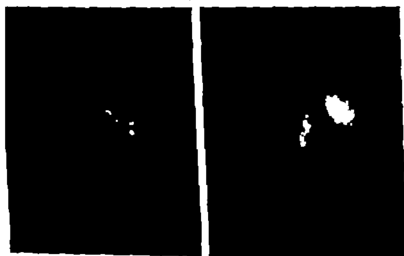

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Table I. *Comparison of the hysterographic and endoscopic findings in 14 cases where the findings were not in agreement*

Group	Findings	No. of cases
I	Hysterographic findings not confirmed by hysteroscopy	4
II	Hysterographic findings confirmed by hysteroscopy but differing in extent	3
III	Hysterographic findings apparently normal but definite changes revealed at hysteroscopy	7

meter of their openings being merely a few millimetres. In the other 2 cases there was radiographic evidence of changes in the *uterine* cavity which resembled polyps. Hysteroscopy carried out 1 and days respectively after hysterography did not confirm their presence despite the fact that good view of the uterine cavity was obtained. Histological examination showed the endometrium to be in the secretory phase in these latter cases. As the cervical and endometrial secretions are ery thick during this phase of the cycle it may have been possible that the changes demonstrated in the hysterograms of these patients represented secretion.

I Group II which comprised 3 cases, extensive adhesions were seen in the hysterogram. In 2 of these cases the endoscopic examination disclosed a band of fibrous tissue which extended from the posterior to the anterior uterine wall and which showed whitish scar-tissue at its base. In the third case ridge was seen on the anterior uterine wall which was about 1 mm high and showed fibrous scar-tissue it did not extend to the posterior uterine all It site corresponded with the filling defect observed in the hysterogram of this patient. These 3 patients were examined by endoscopy 5 30 and 36 days respectively after hysterography I the first cases the changes ppeared to be more extensive in the hysterogram than at endoscopy this may have been due to the accumulation of secretion around the scar tissue. In one of these cases the observation made at the endoscopic examination actually confirmed this assumption.

Group III comprised 7 cases. In 5 of these one or tw polyps were seen during endoscopic examination, the largest being about 4 mm long (Figs. 5 and 6). In another patient, who previously had 10 curettages, endoscopy revealed several whitish scars in the fundus of the uterus and in the seventh case a bluish swelling resembling endometriosis was seen. In 2 of the 5 patients with polyps endoscopy was carried out 1 and 6 months respectively after hysterography and in the other 3 patients 2 days after the procedure.

Twenty-five patients had curettage performed immediately after endoscopy. *Histological* examination disclosed either atrophic or normal endometrium in the secretory or proliferative phase in 16 cases, polyps of the uterine body in 7 cases and localized hyperplasia of the endometrium, resembling metropathia cystica in type, in 2 cases. The findings were consistent with the observations made at endoscopy except for the 7 cases in which the pathologist was unable to detect the polyps seen at endoscopy despite the fact that macroscopic inspection of the curettings strongly suggested the presence of remnants of polyps in most of these cases.

Three patients had hysterectomy *performed*. In 1 patient the uterine cavity did not show any abnormalities and in the other 2 cases ther were submucous fibroids. In all these 3 cases the macroscopic and histological findings corresponded with the observations made at endoscopy

DISCUSSION

Hysterograms may be *difficult to interpret*, particularly if small swellings which protrude into the uterine cavity and resemble tumours are shown. These swellings may represent polyps, submucous fibroids, carcinoma, placentoma, pregnancy a localized swelling of the endometrium, a localized contraction of the uterine wall or accumulations of cervical secretion which are carried into the uterine cavity during the examination. The past history the shape of the swelling and the tone of the uterine wall may be helpful in making the correct diagnosis but differential diagnosis may be difficult. As in many of these cases hysterectomy is not required it is often difficult to confirm or refute the initial diagnosis. This applies also to the cases in which the patient had a curettag., as small polyps may be missed by the curette and the pathologist may have difficulty in differentiating between remnants of benign polyps and normal endometrium. Ob-

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FERTILITY IN PATIENTS WITH OVARIAN ENDOMETRIOSIS BEFORE AND AFTER TREATMENT

Lennart Petersohn

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...mary. 172 patients with endometriosis were investigated. 123 were trying to conceive at the time of treatment. The following are the salient points of the investigation. (1) 64% of the patients with desire for pregnancy at the time of treatment had primary sterility. (2) No correlation between the duration of sterility in years and the development of adhesions was found. (3) The surgical findings were of importance in predicting the success of pregnancy. If only simple endometrial cysts were present, the chance of becoming pregnant after the operation was almost 80%, whereas if cysts and adhesions existed only 40% of patients conceived. (4) The duration of previous sterility was not found to affect the success of pregnancy. (5) The frequency of abortion was markedly reduced after the operation.

In endometriosis, the incidence of sterility approximates 30 to 40% (4), and the disease is found in one-third of infertility laparotomies (3). Turunen, as early as 1938, found that endometriosis is an important cause of sterility (6). In recent years, the treatment has been mainly hormonal, but even nowadays, large chocolate cysts should be treated primarily by surgery, although pseudopregnancy with gestagens in most cases is successful (1). With these facts in mind, I have examined the subsequent fertility of all patients with a diagnosis of ovarian endometriosis who attended the Department of Obstetrics and Gynaecology at the University Hospital in Lund between 1950 and 1964. During these years, the treatment was mainly surgical. The diagnosis of ovarian endometriosis was made by laparotomy or laparoscopy in 554 patients. When the diagnosis was made, 239 were more than 40 years of age; they were excluded from the series. A further 139 less than 41 years of age were excluded because operative measures meant sterilization (hysterectomy, bilateral salpingectomy, bilateral tubal resection or bilateral oophorectomy) or because of other pelvic disease such as chronic salpingitis, or uterine fibroids, i.e. conditions that made it difficult to appraise the role of endometriosis from the standpoint of fertility. Another 4 less than 41 years of age were excluded because the diagnosis in 2 was uncertain and in the other 2 proved to be faulty. The remaining 172 patients made up the series reported below. Questionnaires were sent to the patients by post. All those questioned provided the required information concerning pregnancies and desire for pregnancy. No attempts were made to evaluate the male factor.

MATERIAL

Of the 172 patients, one was aged 14, and the others 21 to 40 years. The average age was 31 years. 73 had conceived before attending the clinic and 6 of these were pregnant at the time of treatment. 168 were treated surgically by unilateral or bilateral ovarian resection, unilateral oophorectomy, breakdown of adhesions, or plastic operation on the tubes. Four were treated with hormones to suppress ovulation, all 4, having only simple endometrial cysts without adhesions, wished to become pregnant later and 3 succeeded.

The material was analysed according to the patients' desire for pregnancy and according to the surgical findings. The latter formed two groups, those with endometriosis with adhesions to other organs (tubes, uterus, bladder, intestine, and pelvic walls) and those without adhesions, but in some with isolated endometrial nodules outside the ovaries. In the tables, the last-mentioned groups are called "cysts + adhesions" and "simple cysts" respectively.

viously there is a need for a hysteroscopic technique which would enable obscure lesions revealed by hysterography to be visualized clearly through the hysteroscope and their true nature to be determined accurately.

Endoscopic examinations of the uterine cavity has so far been carried out on a relatively small scale, probably because the various techniques used did not afford a sufficiently clear view of the uterine cavity. This disadvantage was basically due to the following factors: (i) the uterine cavity could not be distended sufficiently to enable close inspection, and (ii) haemorrhage which hinders clear visualization and endoscopic photography of the uterine cavity could not be prevented (Gribb 1960 amongst others). The endoscope which Silander (1963) evolved was helpful in overcoming these difficulties. However many workers were hesitant to use this technique because they found that the balloon hindered the clear visualization of the uterine cavity despite the fact that it was transparent. Another disadvantage of Silander's technique is that the endometrium is compressed by the balloon, the shape and colour of any existent lesion being thereby modified, and small polyps may therefore easily escape attention.

The clear and viscous dextran solution which we have used in hysteroscopy distends the uterine cavity sufficiently to permit detailed overall inspection. Another advantage of the solution is that it acts as a rinsing solution. The uniform hydrostatic pressure appears to prevent obscuring haemorrhage and any movements of small polyps and aggregations of secretions may be seen through the solution.

The view of the uterine cavity was sufficiently clear to permit also the inspection of the cornua and tubal ostia (Figs. 3–4) and the visualization of the rhythmic contractions of the tubal ostia.

It emerges from this investigation

(i) that hysterography may fail to demonstrate small tumours even if a water-soluble and viscous opaque medium is used and a posterior-anterior, a right oblique, a left oblique, a lateral and an anterio-posterior view are taken.

(ii) that the hysterogram may be difficult to interpret because cervical secretion may be carried into the uterine cavity by the opaque medium and may simulate a lesion or hyperplasia of the endometrium. Moreover secretion may cling to the surface of lesions and thereby modify their contour. As a consequence their size and shape as demonstrated in the hysterogram does not conform to their true size and shape. This appears to have been the explanation in 2 cases of adhesions in this series in which the changes seen in the hysterogram appeared to be more extensive than endoscopy revealed.

(iii) The true nature of a filling defect can be determined by endoscopy alone. This enables the differential diagnosis between polyps and submucous fibroids to be made directly, the diagnosis resting on the shape, colour and vascularity of the tumour and on the appearance of the mucosa over the lesion.

Thus endoscopy of the uterine cavity permitted the determination of the true nature of lesions to be made with greater accuracy than did hysterography.

Admittedly the number of cases examined by the technique described is too small to permit any definite conclusion to be drawn. Moreover only 3 patients had hysterectomy performed and for this reason histological confirmation is lacking in the majority of the cases.

As this series did not include any case of carcinoma it is not possible to comment on the diagnostic value of the modified hysteroscopic technique in these cases. However the modification in our hands, permitted as clear a visualization of the uterine cavity as does macroscopic inspection of a specimen of a bisected uterus.

REFERENCES

Burnett, J. E. Obstet Gynec (NY) *4* 6 1 1964.

Englund, S., Ingelman-Sundberg, A. & Westin, B. Gynaecologia *143* 17 1957

Esposito, A. & Accinelli G. Zbl Gynaek *49* 1671 1966.

Gribb, J. J. Obstet Gynec (NY) 95 593 1960.

Lyon, F. A. Amer J Obstet Gynec *90* 443, 1964

Norment, W. B. Amer J Obstet Gynec *71* 476, 19 6.

— JAMA *160* 1014, 1956

Schmidt-Matthiesen, H. Geburtsh Frauenheilk 26 1499 1966

Silander, T. Acta Obstet Gynec Scand *4* 284, 1963

— Acta Obstet Gynec Scand *4* 300 1963

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ary infertility before the operation was nearly the same in both groups of patients (those with cysts only and those with cysts + adhesions). After treatment, there was still no significant difference between the groups but the frequency of abortion as markedly reduced compared with the frequency before treatment (Table V).

21 patients, 4 of whom had hormone treatment and 17 surgical treatment, only decided that they wanted to conceive some time after diagnosis and treatment. Of the 17 surgically treated patients, 9 did become pregnant on one or more occasions, resulting in 12 deliveries and 1 spontaneous abortion. 26 patients (15%), all surgically treated, did not wish to become pregnant either at the time of treatment or later. Of these 26, 21 had previous pregnancies, resulting in 42 deliveries and 2 abortions.

REFERENCES

1. Chalmers, J. A. Conservative management of endometriosis. Proc Roy Soc Med 61 no. 4, April 1968.
2. Fredriksen, H. Conservative surgery in ovarian endometriosis. Acta Obstet Gynec Scand 32 24 1953
3. Garcia, C. R. Symposium on long-term safety of progestin-estrogen combinations, Absecon, N. J 1964
4. Kistner Robert W Progress in Infertility p. 331 Little, Brown & Co., Boston 1968.
5. Rogers, S. T & Jacobs, W. M.: Infertility and endometriosis. Conservative surgical approach. Fertil Steril 19 529 1968.
6. Turunen, A Endometriosis externa und Sterilität. Acta Obstet Gynec Scand 18, 237 1938.

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Table I *The type of sterility compared with surgical findings in patients trying for a pregnancy at the time of treatment*

	Sterility			Pregnancy attempted for less than 1 year
	primary	secondary	Total	
Simple endometrial cysts	10 53%	9 47%	19	4
Cysts + adhesions	61 66%	31 34%	92	10
Total	71 64	40 36%	111	14

Table II *Duration of sterility in years in patients trying for a pregnancy compared with the surgical finding*

	Duration, years								
	1	2	3	4	5	6	7	8<	Total
Simple endometrial cysts	7	1	4		3	1	0	1	19
Cysts + adhesions	23	9	9	7	15	7	5	17	92

RESULTS

125 of the surgically-treated patients were hoping for a pregnancy at the time of the treatment, 14 (11%) of them had tried to become pregnant for less than 1 year before operation and 6 of these 14 subsequently became pregnant, 3 in the group with and 3 without adhesions. Of the 3 in the adhesion group 2 were in the second and third month of pregnancy at the time of questioning the third had required a Caesarean section for a transverse lie. Of the 3 without adhesions, 1 was in the seventh month of pregnancy the other 2 had required Caesarean sections (one for placenta praevia one for abruptio placentae) Of the other 111 who had been trying for a pregnancy for at least 1 year when first seen, 71 (64%) were complaining of primary sterility and 40 secondary sterility Turunen 1938 found primary sterility in 4–5% of his material (6). No difference was found between the type (primary or secondary) or duration of sterility and the subsequent surgical findings, i.e. simple cysts and cysts with adhesions (Tables I and II).

Of the 111 patients trying for a pregnancy for at least 1 year before treatment 52 (47%) subsequently became pregnant. In 1953 Fredrikson (2) found that of 77 married women under forty in whom the child-bearing functions were preserved, 30 (38.9%) became pregnant after surgical treatment for endometriosis. In 1968 Rogers & Jacobs (5) published a figure of 63%. Of the patients in the present series, with only simple endometrial cysts, 15 (79%) became pregnant after the operation, whereas 37 (40%) with cysts + adhesions became pregnant. The difference is significant on the 99.0% level (Table III). The duration of the involuntary sterility was not found to affect the prospects of pregnancy after the operation (Table IV).

The frequency of abortion in those with second-

Table III *Fertility after treatment in patients earlier sterile*

	Pregnancy		Non-pregnancy		Total
Simple endometrial cysts	15	79	4	21	19
Cysts + adhesions	37	40	55	60	92
Total	52	47	59	53	111

$p < 0.01$

Table IV *Sterility duration in years compared with pregnancy prospects*

	Duration, years								
	1	2	3	4	5	6	7	8<	Total
Pregnant	18	6	3	6	8	3	3	4	51
Non-pregnant	11	5	10	3	10	5	2	14	60

Table V *Number of pregnancies and abortions before and after treatment compared with surgical findings*

	Before treatment			After treatment		
	Pregnancies	Whereof abortions		Pregnancies	Whereof abortions	
Simple endometrial cysts	26	7	27	26	3	12
Cyst + adhesions	65	13	20	58	4	7
Total	91	20	22	84	7	8

Abortion frequency significantly lower after treatment. $p < 0.01$

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Abortion frequency significantly lower after treatment $p < 0.01$

Acta Obstet Gynec Scand 49 335–341 1970

EXPERIENCES WITH PARACERVICAL BLOCK

A Double-blind Study with Bupivacaine (Marcaine®)

Hans Westholm, Ricardo Magno and Anders Å-son Berg

From the Department of Obstetrics and Gynaecology (Head Professor Sam Brody), University of Gothenburg, and the Department of Anaesthetics I (Head K.-G. Dhuner M.D.), Sahlgrens Hospital Gothenburg, Sweden

Abstract The authors have studied paracervical blocks with bupivacaine, physiological saline and bupivacaine with adrenalin 1 200 000 by means of a double-blind technique.

The analgesic effect was good in nearly 80% of the cases with active substance and in about 20% of the cases with physiological saline. The duration of analgesia was shorter when physiological saline was used. No important difference in duration of analgesia was found between bupivacaine and bupivacaine-adrenalin. Adrenalin did not seem to improve the effect when added to bupivacaine.

The dilatation of the cervix was no more rapid when active substance was used than with physiological saline. Bupivacaine-adrenalin seemed to be associated with more uterine inertia than bupivacaine and physiological saline.

Foetal bradycardia was found in 4%. 2 of the 8 cases of foetal bradycardia were after blocks with physiological saline. All these 8 foetuses were born with Apgar scores of 10. In the whole study there were no Apgar scores below 8.

A few maternal complications of short duration were recorded, all when bupivacaine-adrenalin was used.

The authors have the impression that paracervical block is not entirely free from risks. Foetal complications may be expected.

One case of foetal death, possibly connected with paracervical block using bupivacaine-adrenalin is described.

The paracervical block (PCB) in obstetrics was first described by Gellert in 1926. During the last few years, obstetricians have shown more interest in the technique. Good results have been reported (5, 8, 9, 12, 14, 20), but also undesirable side-effects on the foetus (21) and on the mother (4, 15) have been noted.

At Sahlgrenska Sjukhuset, Department of Obstetrics and Gynaecology, PCB has been used to a relatively large extent during the last 4 years. More than 1 500 blocks have been given.

MATERIAL AND METHOD

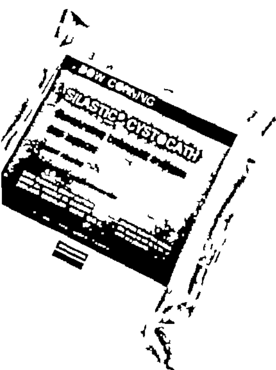
The series consists of 195 randomly selected patients. PCB was performed both day and night, and the sole indication was the need to relieve pain.

Three different agents were used, bupivacaine 0.25% without adrenalin (Marcaine®), bupivacaine 0.25% with adrenalin 1 200 000, and physiological saline as placebo. Each of these agents was given to approximately equal numbers of primigravidae and multigravidae. The usual double-blind technique was used.

The blocks were performed by Kobak's technique with few modifications. The patients were lying on their backs on the delivery beds, legs drawn up without support. The Kobak needle was directed with the help of the palpating hand to the vaginal fornix and 10 ml were injected on each side at 3 and 9 o'clock positions. The injections were given between two uterine contractions. All the blocks were performed when cervical dilatation was about five cm. The foetal heart rate was checked before the block, for at least 5 min or during and between three consecutive contractions. The frequency and the duration of the contractions were noted. After the blocks both mother and foetus were carefully observed for 20 min. Later on the observation was carried out by the midwives, every 15 min. The cervical dilatation was followed by means of vaginal examination 1 and 2 hours after the block. The analgesic effect and duration of analgesia were studied as well. We also noted the need for oxytocics or for additional analgesics, and possible maternal or foetal complications.

We have tried to avoid repeating the blocks. Whenever the effect was not sufficient the patient was allowed to inhale a mixture of 50% nitrous oxide in oxygen, later [illegible]. We have also tried to avoid the use of narcotic analgesics as much as possible.

All the babies were born at term. All of them were born in the occipito-anterior position.



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Abstract. The authors have studied paracervical blocks with bupivacaine, physiological saline and bupivacaine with adrenalin 1 200 000 by means of a double-blind technique.

The analgesic effect was good in nearly 80% of the cases with active substance and in about 20% of the cases with physiological saline. The duration of analgesia was shorter when physiological saline was used. No important difference in duration of analgesia was found between bupivacaine and bupivacaine-adrenalin. Adrenalin did not seem to improve the effect when added to bupivacaine.

The dilatation of the cervix was no more rapid when active substance was used than with physiological saline. Bupivacaine-adrenalin seemed to be associated with more uterine inertia than bupivacaine and physiological saline.

Foetal bradycardia was found in 4%. 2 of the 8 cases of foetal bradycardia were after blocks with physiological saline. All these 8 foetuses were born with Apgar scores of 10. In the whole study there were no Apgar scores below 8.

A few maternal complications of short duration were recorded, all when bupivacaine-adrenalin was used.

The authors have the impression that paracervical block is not entirely free from risks. Foetal complications may be expected.

One case of foetal death, possibly connected with paracervical block using bupivacaine-adrenalin is described.

The paracervical block (PCB) in obstetrics was first described by Gellert in 1926. During the last few years, obstetricians have shown more interest in the technique. Good results have been reported (5, 8, 9, 12, 14, 20), but also undesirable side-effects on the foetus (21) and on the mother (4, 15) have been noted.

At Sahlgrenska Sjukhuset, Department of Obstetrics and Gynaecology, PCB has been used to a relatively large extent during the last 4 years. More than 1 500 blocks have been given.

MATERIAL AND METHOD

The series consists of 195 randomly selected patients. PCB was performed both day and night, and the sole indication was the need to relieve pain.

Three different agents were used, bupivacaine 0.25% without adrenalin (Marcaine®), bupivacaine 0.25% with adrenalin 1 200 000, and physiological saline, as placebo. Each of these agents was given to approximately equal numbers of primigravidas and multigravidas. The usual double-blind technique was used.

The blocks were performed by Kobak's technique with few modifications. The patients were lying on their backs on the delivery beds, legs drawn up without support. The Kobak's needle was directed with the help of the palpating hand to the vaginal fornix and 10 c.c. were injected on each side at 3 and 9 o'clock positions. The injections were given between to uterine contractions. All the blocks were performed when cervical dilatation was about five cm. The foetal heart rate was checked before the block, for at least 5 min or during and between three consecutive contractions. The frequency and the duration of the contractions were noted. After the blocks both mother and foetus were carefully observed for 20 min. Later on the observation was carried out by the midwives, every 15 min. The cervical dilatation was followed by means of vaginal examinations 1 and 2 hours after the block. The analgesic effect and duration of analgesia were studied as well. We also noted the need for oxytocics or for additional analgesics, and possible maternal or foetal complications.

We have tried to avoid repeating the blocks. Whenever the effect was not sufficient the patient was allowed to inhale a mixture of 50% nitrous oxide in oxygen, intermittently. We have also tried to avoid the use of narcotic analgesics as much as possible.

All the babies were born at term. All of them were born in the occipito-anterior position.

Table I *Analgetic effect*

		No of cases		
		Bupivacaine	Bupivacaine–Adrenaline	Phys. saline
Good effect	Primip.	32	30	8
	Multip.	19	22	7
	Total	51	52	15
Failures	Primip.	5	8	26
	Multip.	8	7	23
	Total	13	15	49

RESULTS

Analgesic effect

The more subtle classification of the analgesic effect into, for example, "excellent" "good" "fair" etc. proved rather difficult. We therefore decided to judge the analgesia effect of the block as just "good" or failures" By "good" effect is meant that the patient became completely free from pain both during and between the contractions. All other cases were coded as "failures" even if some of them experienced relatively good relief from their pain. A unilaterally effective block was also coded as a failure" The analgesic effects and the composition of the series is shown in Table I.

The effect of the PCB with bupivacaine was good in 51 out of 64 patients. Bupivacaine adrenalin gave good effect in 52 patients out of 67 The effect of saline was good in 15 out of 64 patients. No difference could be noted either between primigravidas and multigravidas or between bupivacaine with and without adrenalin Thus good analgesia was produced in about 80% of the cases given active substance and in about 24% given placebo. The difference between these two groups is statistically significant.

Duration of analgesia

In many cases it was impossible to measure the maximal duration of analgesia. This was the case when patients were delivered in a persisting analgesic state or when after complete cervical dilatation pains resulted from distension of perineum. In these conditions the minimal duration was measured. In each case the duration was counted to the nearest quarter of an hour

In 59 cases the maximal duration could be measured and in 67 cases an assessment could not be made. Thus it was possible to measure maximal duration only in 14 out of 48 multigravidas. One multiparous patient got an unilateral block which could be measured. Among primigravidas, who usually have slower deliveries, it was possible to measure the maximal duration in 45 out of 70. Seven primigravidas got unilateral blocks with measurable maximal duration. The results with regard to maximal duration are shown in Table II. Minimal durations are given in Table III.

The duration of the analgesia was found to be shorter after a placebo than when local anaesthetic was used. The longest duration of analgesia

Table II *Maximal duration (hours)*

Time (hours)	Agent					
	Bupivacaine		Bupivacaine–Adrenaline		Phys. saline	
	Primip.	Multip.	Primip	Multip.	Primip.	Multip
¼						
½	1	1	3	1	1	1
¾						
1	4	1	2	1	4	
1¼		1				
1½			3	1		
1¾			1			
2	3		2		1	1
2½	2	1	1			
3	3		3			
3½	3		3	1		
4	1		2			
Median	2	1 1½	2	1½	1	1

Table III *Minimal duration (hours)*

Time (hours)	Agent					
	Bupivacaine		Bupivacaine–Adrenaline		Phys. saline	
	Primip.	Multip	Primip.	Multip	Primip	Multip
¼		1				
½		3		1		
¾	1	3		2		1
1	4	3	1	4	1	
1¼	1	4		3		1
1½		1	1	3	1	
1¾	1		1			1
	3		4			
½	1	1	2			
3				1		
3½			1			
4	1					
Median	1½	1		1½	1½	1½

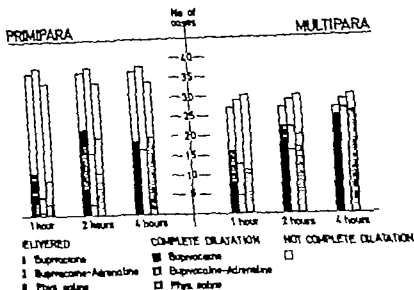


Fig. 1 Cervical dilatation

fter a placebo was, in 2 cases, more than 2 hours. The difference in duration between solutions of ocal anaesthetics containing adrenalin and solutions without adrenalin was relatively slight. The duration of both agents varied from $^1/_2$ hour to 4 hours. In those cases where maximal duration could be measured the median time in multigravidas was 2 hours with both the active agents. In multigravidas, as expected, the median time was shorter 1 / hours with bupivacaine and 1 hours with bupivacaine–adrenalin. The number of patients in these groups is too small for statistical analysis. The addition of adrenalin to bupivacaine does not seem to be of definite value for prolonging the duration of the paracervical block.

The speed of cervical dilatation

We could follow the effect of PCB upon cervical dilatation by means of two vaginal examinations 1 and 2 hours respectively after the administration of the block. The results ar demonstrated in Fig 1

No differences could be noted among the multigravidas. The speed of dilatation was uniform, and approximately the same number of patients were delivered 1 and 2 hours after PCB, irrespective of the injected agent. Among the primigravidas the speed of dilatation was not affected by PCB either. On the other hand there was reduction in the number of deliveries hours after PCB with bupivacaine–adrenalin: 3 patients out of 38, in comparison with 7 out of 37 among the bupivacaine group and 11 out of 34 among saline group.

The time between PCB and spontaneous delivery was checked. No differences could be found between the three agents within the multigravidas. A statistically significant difference ($p < 0.05$ t-test) was found between the results for bupivacaine–adrenalin and saline, in the primigravidas, the delivery times being shorter with saline. Results are shown in Table IV

Side-effects

Uterine inertia

W considered uterine inertia to be present in those cases where after PCB the frequency of contractions fell to below ten per hour or whenever cervical dilatation was unchanged for 1 hour It is worth mentioning that in several cases not classified as uterine inertia a short state of uterine

Table IV *Times in minutes between PCB and spontaneous delivery (means ± S.D)*

Agent	Primipara	Multipara
Bupivacaine	240±130	103±78
Bupivacaine–Adrenaline	278±100	116±61
Phys. saline	191±111	126±97

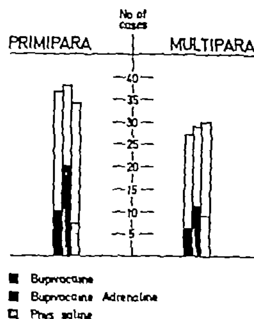


Fig. Uterine inertia.

inactivity was noticed, for about 15 to 20 min followed spontaneously by complete restoration of normal contractions.

Inertia was found in 16 patients out of 64 in the bupivacaine group, in 31 out of 67 in bupivacaine–adrenalin group and in 16 out of 64 with saline. No significant difference between primigravidas and multigravidas was noted. On the other hand a statistically significant difference was found between the bupivacaine–adrenalin group and the two others (χ square, $p < 0.05$). This may be explained as the result of a negative effect of bupivacaine–adrenalin upon the contractile activity of the uterus.

Oxytocics were needed in 9 cases out of 64 in the bupivacaine group in 12 cases out of 67 in the bupivacaine–adrenalin group and in 5 cases out of 64 in the saline group. No significant difference was found between primigravidas and multigravidas or between the agents used.

Table V. *Foetal bradycardia*

Agent	Primipara	Multipara
Bupivacaine	1 case -5 min	1 case 5 min
Bupivacaine Adrenaline	1 case -5 min	3 cases 5 min 15 min 55 min
Phys. saline	cases 40 min 10 min	

Effect on the foetus

In 8 cases out of 195 foetal bradycardia was found in direct relationship to PCB without an other possible explanation. Only cases where the foetal heart rate was under 100 per minute for at least 5 min or during and between three consecutive contractions were recorded as foetal bradycardias. The bradycardia in several cases lasted much longer. Slight bradycardias during very short periods were noted as well. The distribution of bradycardias and their duration are shown in Table V. Seven of the foetuses with bradycardia were later born with an Apgar score of 10 after 1 min and one child had an Apgar score of 9. No cases of tachycardia over 160 per minute were noted. The foetal heart rate after delivery was closely observed. None of 195 infants had Apgar scores below 8. 16 of them had 8 or 9, all the others had 10.

Vacuum Extractions

A total of 13 patients were delivered with the Vacuum Extractor (V.E.). In _ cases the V.E. was used after serious bradycardia, which could be related to PCB. Both cases were multigravidas and belonged to the bupivacaine–adrenalin group.

Case Descriptions

Case 1. 3 year-old patient, gravida II, with a normal delivery 1961. Soon after PCB, the foetal heart rate decreased from 140 to 170 min. 15 min later a rate of 9 min as noted. During the following 30 min the heart rate varied between 9 and 75/min. When the frequency dropped to 70/min, extraction with V.E. was arranged. The patient had good analgesia all the time. Cervix was dilated to 8 cm. Clear amniotic fluid was found after rupture of the membranes. A vacuum extraction with V.E. was performed using additional pudendal anaesthesia, about 1 hour and min after PCB. No umbilical cord complications were noticed. Immediately after delivery the infant's heart rate was only 80/min and the Apgar score 9. T minutes later heart rate became 110/min. Weight 3 900 grams.

Case 6-year-old patient, gravida II, with normal delivery 1965. PCB with good effect. Foetal heart rate unexpectedly diminished to 80/min. 3 min after PCB, the cervix was fully dilated, and pudendal block was performed. Delivery 3 min after PCB with V.E. No cord complications were noted. After 1 min the Apgar score was 10. Weight 3 _80 grams.

The remaining 11 patients are delivered with V.E. for other indications not related to PCB.

Side effects in the mothers

In 2 patients given bupivacaine, numbness of the legs was noted. Among those given bupivacaine-adrenalin there were 3 cases of pronounced pallor, 1 case with paleness and dyspnoea, 1 case with headache and 2 cases with numbness of the legs. With saline, no side effects were observed. Thus the majority of side effects occurred in the bupivacaine-adrenalin group but all symptoms were slight and transient and no changes in blood pressure and maternal heart frequency were observed.

DISCUSSION

Analgesic effect

The frequency of good analgesia of about 80% corresponds relatively well to that found by others (, 8, 9 12, 15 16, 20). It is possible that the frequency of good analgesia can be improved if the paracervical injection of the local anaesthetic drug is made at two sites bilaterally corresponding to 3 and 4 o clock and 8 and 9 o clock respectively (20, 21), but it has been shown that X-ray contrast spreads in the pelvis in the same way when injected "paracervical" and "uterosacral" (13). The placebo-effect of 24% of the cases is rather high but others have reported placebo-effects from 12 to 24% (14 17). In order to reduce the effect of suggestion, the patients were informed that the injections should only contribute to relax and open the cervix. However later on the method became more commonly known by the patients, and then many of them expected pain relief, which made their reactions less reliable.

Other authors have shown that bupivacaine has a long duration of action when used in other types of regional block (1). In paracervical blocks too, bupivacaine has longer duration than other available local anaesthetics (9 11 20).

The speed of dilatation

Differences in speed of dilatation could not be observed. According to Fig. 1, in primigravidas given bupivacaine-adrenalin the progress of labour was slower after 2 hours than in those given bupivacaine or saline. However this difference is compensated for after 4 hours. A possible interpretation of this is that bupivacaine-adrenalin causes a temporary uterine inertia.

Uterine inertia

Uterine inertia according to our definition occurred most commonly when we used bupivacaine-adrenalin. Our estimate of the type of labour must be regarded as subjective as we did not use a tocograph. It has been known for a long time (14) that adrenaline, injected in addition to local anaesthetics, weakens uterine contractions when injected paracervically. Even local anaesthetics themselves may have a depressing effect on labour (22). This may be a direct (local) effect on the uterine muscle or due to a blockage of nervous impulses to the uterus. Uterine contractions may diminish both in intensity and frequency and even disappear for a while (14 17). In our investigation, however bupivacaine without adrenalin did not cause more uterine inertia than saline.

Side effects in the mother

The side effects noted in the mothers were slight and transient. Except for numbness of the legs, the effects were interpreted as those of adrenalin. Other authors have found more serious complications such as haematomas, parametritis, cramps and collapse (3 15). Complications in the mothers have been considered as resulting from unintentional intravenous injections (4). High concentrations of local anaesthetics have been found in the maternal blood shortly after the block. The sleep which sometimes is observed in mothers after PCB is considered not just to occur because the mother is tired and free from pain, but to be a direct effect of the local anaesthetic on the central nervous system.

Foetal bradycardia

The frequency of foetal bradycardia in this series is 4%. In other investigations with different local anaesthetics, with or without adrenalin the frequency varies from 2–30% (2, 5 10, 21). Some authors have not found any foetal complication such as bradycardia (18). We are aware that we could have failed to observe some changes in the foetal heart rate as we used ordinary auscultation. However we have not overlooked those cases where a more pronounced bradycardia appeared during the first 20 min. Other factors such as

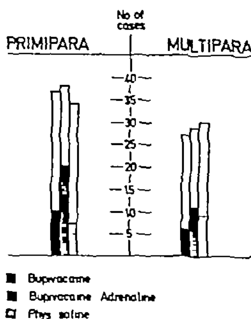


Fig Uterine inertia.

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Table V *Foetal bradycardia*

Agent	Primipara	Multipara
Bupivacaine	1 case 25 min	1 case 5 min
Bupivacaine–Adrenaline	1 case ~5 min	3 cases 5 min 15 min 55 min
Phys. saline	cases 40 min > 10 min	

Effect on the foetus

In 8 cases out of 195 foetal bradycardia was found in direct relationship to PCB, without any other possible explanation. Only cases where the foetal heart rate was under 100 per minute for at least 5 min or during and between three consecutive contractions were recorded as foetal bradycardias. The bradycardia in several cases lasted much longer Slight bradycardias during very short periods were noted as well. The distribution of bradycardias and their duration are shown in Table V Seven of the foetuses with bradycardia were later born with an Apgar score of 10 after 1 min and one child had an Apgar score of 9 No cases of tachycardia over 160 per minute were noted. The foetal heart rate after delivery was closely observed. None of 195 infants had Apgar scores below 8 16 of them had 8 or 9 all the others had 10

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when considering adrenalin as an addition to bupivacaine for paracervical block.

According to our experience (and that of others) one can expect foetal complications, which are sometimes serious, when paracervical blocks are used in obstetrics. In many cases, however the block is of great value, for instance in mothers with severe pain or with cervical dystocia, where rapid relief and dilatation is easily obtained. Routine administration to patients in moderate pain is of doubtful value considering the risks described

ACKNOWLEDGEMENT

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REFERENCES

1 Albert, J & Löfström, B Bilateral ulnar nerve block for the evaluation of local anaesthetic agents. Acta Anaesth Scand 9 1, 1965.
2. Cooper, K., Gilroy K J & Hurry D. J Paracervical nerve block in labour using bupivacaine (Marcaine). J Obstet Gynaec Brit Comm 75 863, 1968.
3 Cooper K & Moir J. Ch Paracervical nerve block: simple method of pain relief in labour Brit Med J 1 1372, 1963.
4 Evans, J A Chastain, G. M. & Phillips, J M.. The use of local anesthetic agents in obstetrics. Southern Med J 62 519 1969
5 Gad, C Paracervical block Acta Obstet Gynec Scand 46 7 1967
6. Gomez, D. F Paracervical block in obstetrics. Lancet 7604 1163, 1969
7 Goodman, L. S & Gilman, A The pharmacological basis of therapeutics, 3rd edn Macmillan, New York, 1965
8 Gudgeon, D H Paracervical block with bupivacaine 0 25% Brit Med J 2 403, 1968.
9 Hedberg, G & Hokegård, K H Paracervikal bedövning vid förlossningar. Läkartidn 63 3649 1966
10 Holmala, A Ojala, A & Korhonen, M Paracervical blockade with Marcaine-adrenaline Acta Anaesth Scand 13 1 1969
11 Hokegård, K.-H Erfarenheter av paracervikal bedövning vid förlossningar Läkartidn 65 3127 1968
12. Jenzo, H J. Der paracervicale Block zur Geburtserleichterung Gynaecologia 165 309 1968
13 Kobak A J Sadove, M S & Mazeros, W T Anatomic studies of transvaginal regional anesthesia. Obstet Gynec 19 302, 1962.
14 Pitkin, R. M & Goddard, W B Paracervical and uterosacral block in obstetrics. Obstet Gynec 21 737 1963
15 Salohemo A. M Paracervical block anesthesia in labour Acta Obst Gynec Scand XLVII, suppl. 5, 1968
16. Scott, D. B Galloway R. K., Lees, M. M. & Livingstone, J R. B.. Bupivacaine in paracervical block. Proc Roy Soc Med 61 1158, 1968.
17 Seeds, A. E., J Stein-Messinger P & Dorsey J. H.: Paracervical blocks: results of double-blind evaluation. Obstet Gynec 20 462, 1962.
18. Saley J E. & Gold, E. M.. Paracervical block in the management of labor Obstet Gynec 27 116, 1966.
19 Sinclair J C, Fox, H. A., Lentz, J F Fuld, G. L. & Murphy J Intoxication of fetus by local anesthetic: Newly recognized complication of maternal caudal anesthesia. New Engl J Med 273 1173, 1965.
20. Stockhausen, H.: Erfahrungen mit einem neuen Lokalanaesthetikum bei der Paracervikalblockade. Dtsch Med Wschr 92 2220, 1967
21. Teramo, K. & Widholm, O.. Studies of the effect of anaesthetics on foetus. Part 1. The effect of paracervical block with mepivacaine upon foetal acid-base values. Acta Obstet Gynec Scand XLVI, suppl. 2, 1967
22. Zourlas, P A. & Kumar D An objective evaluation on paracervical block on human uterine contractility Amer J Obstet Gynec 91 217 1965

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pressure on the foetal skull when the block is administered may be responsible for some bradycardias (6). However these bradycardias are neither pronounced nor long lasting

The cause of the bradycardia is unknown Adrenalin added to the local anaesthetic has been considered responsible by provoking vasoconstriction in the placenta and the myometrium with impairment of the foeto-maternal gas exchange and resultant foetal hypoxia (9) This explanation is not sufficient as it has been demonstrated that bradycardia occurs even without adrenalin (14). Local anaesthetics may easily pass the placental barrier because the injections are given near to the uterus and possibly quite often intravenously (4) High foetal blood concentrations of local anaesthetics have been found following injections of the anaesthetic drug (4).

If one considers the local anaesthetic as the cause of the foetal bradycardias the frequency might be reduced if adrenalin is added to the local anaesthetic in order to reduce the rate of absorption. Evidently this is not the case in the highly vascular paracervical tissues in pregnancy In this series the frequency of bradycardia was not lower when adrenaline was added.

Metabolic acidosis in the foetus has been found in connection with bradycardia with lowering of the pH and base excess and rising pCO_2 (21).

Four cases of serious bradycardia are recorded following accidental puncture of and injection into the scalp of the foetus during attempted caudal anaesthesia (19). The foetal ECG showed idioventricular rhythm with a prolonged intraventricular conduction time This finding agrees with the opinion that local anaesthetics have a quinidine-like effect on the myocardium with bradycardia as a consequence (7).

In our series there are 2 cases of pronounced bradycardia following paracervical block with saline The interpretation of this finding is, however difficult because it is well known that spontaneous unexplained bradycardia is encountered from time to time.

After this study we continued using bupivacaine-adrenalin for PCB with good effect. However changes in the foetal heart rate were often observed mostly of a minor and transient nature.

Among the newborn infants we had not, until 1969 in any of the 1 500 cases where we used PCB found any neonatal asphyxia due to the block, nor had we had any infant mortality The drugs used were mepivacaine, 1 % mepivacaine 1 % with adrenalin 1 200 000 bupivacaine $^1/_4$ and bupivacaine $^1/_4$ % with adrenalin 1 200 000 In 1 case in 1969 however following a PCB we had a serious foetal bradycardia and the infant was born dead.

Case Description

The mother was a 19-year-old gravida II, who 4 years earlier had an abortion in the 2nd month of pregnancy In the first trimester of the present pregnancy the patient had been given ECT electro-convulsive therapy for depression and after this she had been treated with Sobril® and Saroten® for a couple of months. The patient suffered from moderate psychiatric symptoms during the whole pregnancy The course of pregnancy was otherwise normal and she was seen at regular intervals. The patient entered the delivery ward in good labour 8 days after expected term. After 4 hours of labour the patient began to suffer from pain. The cervix was dilated to 5 cm. Paracervical block was administered with 10 ml bupivacaine-adrenalin on both sides with good analgesic effect. 5 minutes later the foetal heart rate was 76 min. As the heart rate did not return to normal the infant was delivered with V.E. The procedure lasted 8 min, the mother had strong contractions during the delivery and the foetal heart rate were 60 min between the contractions. The membranes had ruptured 40 min after administration of the block and the amniotic fluid was clear Immediately before the extraction the amniotic fluid became meconium stained. The child was born occipito-posterior 1 hour 8 minutes after administration of the block. The child showed no signs of life and attempts at resuscitation were in vain.

At autopsy nothing was found that could explain the death. The placenta was mature with minimal regressive changes. The child had no congenital anomalies. No intracranial haemorrhage was found. Reactions for toxoplasmosis and listeriosis were negative. We cannot exclude the possibility that the block contributed to the intrauterine death.

COMMENT

This investigation has confirmed that bupivacaine has a lengthy influence when used as a paracervical block. The addition of adrenalin 1 200 000 to bupivacaine does not seem to be of definite value in prolonging the duration of the paracervical block However when adrenalin is added it seems to give the following undesirable effects: increased incidence of uterine inertia in primigravidas, increased frequency of foetal bradycardia, and certain circulatory side effects in the mothers. Consequently we are rather cautious

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CERVICAL CERCLAGE IN THE TREATMENT OF INCOMPETENT CERVIX

A Retrospective Analysis of the Indications and Results of 164 Operations

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Abstract. Between 1959 and 1968 cervical cerclage operation was performed 163 times in 159 cases because of assumed cervical incompetence. The operation was carried out during pregnancy 156 times, and 3 times in a nonpregnant patient. 4 women had two operations during the same pregnancy. The operations represent 1 in 104 deliveries at the hospital during the study period. The diagnosis of cervical incompetence was based on the history of previous pregnancies in 99 cases (79%). The finding of a short and open cervix was made 85 times (68%), and the diagnosis was supported by the hysterographic findings in 11 cases (9%). The average duration of gestation at the time of operation was 14 weeks, and the average total duration of the pregnancies was 35 weeks. The previous foetal salvage rate was 30.8%, and the final success rate 80.2%. The comparable rates for normal deliveries without cervical cerclage at the same time were 74.7%, and 97.1%, respectively. The abortion rate in the series after treatment was 13.6. Premature deliveries with loss of the child occurred 4 times, leading to a perinatal mortality rate of 3.2%. Breech presentation was found 10 times (6.3%). Caesarean section was undertaken 23 times (18%) in 21 patients. The ratio of the final success rate and the previous foetal salvage rate (foetal salvage ratio) in the whole series was 2.7 and in the randomly selected cases 1.1. This ratio was the highest (3.8) between 26 and 30 years, and when the operation was performed between the 16th and the 19th week of pregnancy (3.3). The maximum benefit rate of the operation was 30% [80.2 − 30.8 − (97.1 − 74.7)]%. This rate is little affected by unnecessary operations, but the difference between the foetal salvage ratios in the operation and the control materials is greatly affected by them. This difference was 1.4 (2.7 − 1.3) in this material. The differences in abortion rates, laws and standards of obstetric care lead to differences in the materials. Therefore the following criteria are suggested to be included in the reports concerning cervical cerclage operations:

(1) Number of operations per number of deliveries in the study period
(2) Final success rate of the series
(3) Previous foetal salvage rate
(4) Foetal salvage ratio (the ratio of no. 2 and no. 3)
(5) Final success rate and previous foetal salvage rate among the mothers without cervical suture in the same hospital at the same study period
(6) Foetal salvage ratio from no. 5
(7) Difference between foetal salvage ratios in the operation and the control groups
(8) Maximum benefit rate in the operation material

Cervical incompetence is generally accepted as a cause of middle trimester abortions and premature labour. According to Mann et al. (5) cervical incompetence is the cause of about 20% of late habitual abortions, and in 0 % of all abortions. First contributions to the diagnosis and the correction of this state were made by Palmer & Lacomme (7), and by Lash & Lash (4), who operated in the nongravid state. Shirodkar (8) and McDonald (6) carried out the repair during pregnancy.

The characteristic history of a patient with cervical incompetence is one where two or more middle trimester abortions have occurred painlessly and usually following rupture of the membranes. It has been suggested that the diagnosis of incompetence in the nonpregnant cervix can be made by the passage of a no. 9 Hegar dilator through the cervix, by traction test with a filled Foley catheter or by hysterography. However none of these is considered to be an absolute indicator of cervical incompetence.

In the original Shirodkar operation the encircling ligature was obtained from the fascia lata of the patient' thigh. Currently synthetic dacron ligature (Mersilene) has become widely adopted, as it may easily be removed at the onset

encountered 4 times, leading to a perinatal mortality rate of 3.2%. In the group where the child was lost, the previous foetal salvage rate was 26.7% (20 living infants and 55 which were lost).

The results of cerclage operations at different stages of pregnancy are shown in Table II, where attention has been paid to the previous obstetric record in each group. The foetal salvage ratio was highest (3.3) in the group where the operation was performed between the 16th and the 19th pregnancy weeks.

The average age of the patients was 29 years. The foetal salvage ratio was highest (3.8) in the group of 6–30 years. The foetal salvage ratio in the whole series was 2.7 while it was 1.3 in the series of 100 randomly selected patients at the same hospital during the study period.

Congenital abnormalities of the uterus were confirmed in 7 cases: 4 had uterus duplex and 3 had uterus bicornis unicollis. 3 had been operated on by the method of Strassman (9). One child was lost in this group, due to abruption of the placenta.

Carcinoma of the cervix was found in one pregnant woman. The preliminary diagnosis of carcinoma in situ was based on a biopsy from the portio. Amputation and conisation of the cervix were performed at the same time as the cervical cerclage. Histological examination revealed an infiltrative growth of malignant tissue. At the 37th week of the pregnancy the child was delivered by caesarean section, which was completed by radical hysterectomy according to Wertheim (11). In all, caesarean section was carried out ,3 times (18.4%) in 21 patients. Breech presentation was observed 10 times (6.3%). There were no severe maternal complications in the series.

DISCUSSION AND CONCLUSIONS

The patients represent 1 in 404 deliveries at the hospital during the study period. This indicates far too high a frequency f the cervical operation in relation to normal deliveries. Great variations in this ratio have been reported, and the figures quoted by Danforth (2) are near the average. He carried out 7 operations in 3 years among 6 000 deliveries, which gives a ratio of 1 in 850 deliveries.

In this study the foetal salvage rate was increased from 30.8% to 83.2% in the pregnancies where a cervical cerclage was made. A random sample of 100 obstetric patients from the study period in the same clinic gave a previous foetal salvage rate of 74.7% and the final success rate of 97.1%. This improved salvage of 22.4% in the control series may also have occurred in our group treated for cervical incompetence, indicating foetal loss due to reasons other than cervical incompetency. Anyway it seems that the obstetric history is the basic criterion for the diagnosis of cervical incompetence.

Table III *Relation of the patient s age to the foetal salvage ratio (final success rate per previous foetal salvage rate)*

Age (years)	No.	Final success rate ( )	Previous foetal salvage rate (%)	Foetal salvage ratio
Below 25	25	80.0	28.4	2.8
26–30	48	85.4	22.8	3.8
31–35	37	78.4	38.5	2.0
36–40	11	90.9	39.3	2.3
41–45	1	0.0	100.0	

The data of Floyd (3) support the concept that cervical dilatation alone cannot confirm the diagnosis of cervical incompetence, as in 72% of multigravidas there was 1–3 cm cervical dilatation at the 6th month s pregnancy. It is probable that in our series number of the operations were unnecessary where the finding of a short and open cervix was the only indication for the operation.

Finally complicated pregnancies tend to be concentrated in a University Hospital, a fact which certainly contributes to our high frequency of cervical cerclage operations.

The application of the foetal salvage ratio of the present and previous pregnancies allows a better evaluation of the benefit from the operation than does the use of the final success rate alone. This is illustrated in Fig. 1 where the fairly high final success rate shows rather small variations at different stages of gestation. The use of this ratio gives also the advantage of including the effect of previous obstetric history in the evaluation of the results. Large series are necessary in order to define the most favourable time for the operation. When the benefit of such an operation is evaluated, the effect of previous foetal loss occurring in normal multiparae in the

Table I *History of previous pregnancies in the series of 125 patients with cervical cerclage operation*

	Previous deliveries						
	0	1	2	3	4	5	Total
Previous abortions							
0	1	9	3	1	—	—	14
1	5	12	5	5	1	—	28
2	13	13	3	1	1	—	31
3	10	14	1	2	—	—	27
4	7	4	1	—	—	—	12
5	5	3	2	—	—	—	10
6	—	1	—	1	1	—	3
Total	41	56	15	10	3	—	125

of labour or when abortion is inevitable. The original idea of placing the encircling ligature around the cervix by th vaginal route has main tained its popularity although other methods have also been described. A transabdominal cervico-uterine cerclage was used by Benson & Durfee (1). Total cervical closure was suggested by Szendi (10)

The present paper describes and evaluates the indications and the results of the cervical cerclage operations performed by the vaginal route during a 10 year period at the University Central Hospi tal Helsinki.

MATERIAL AND METHODS

Th. peration f cervical cerclage was carried out in 159 women between 1959 and 1968 during 156 pregnancies, and 3 f the women had the operation while in the non-pregnant state The operation was performed twice du ing the same pregnancy in 4 cases. The total number of deliveries at the same hospital in the study period was 64 198 Th: complete records of 1_5 patients could be obtained.

The diagnosis of cervical incompetence was based on the previous obstetric history and on the changes in the cervi In all, 111 of the patients (89 %) had one or more previous abortions. The history of 99 patients (79) indicated cervical incompetence and this was the main reason for the operation in 30 cases (4). The previous obstetric histories are compiled in Table I.

A short and open terine cervix was present in 85 patients (68), and it as the main reason for the operation in 17 cases (14). In 11 patients (9) the diagnosis was confirmed by hysterography in a nongravid state The hysterographic finding was considered to be the main reason for the operation in 8 cases (6 %).

The foetal salvage rate of previous pregnancies in this series was 30.8 % (128 li ing infants and _87 which were lost). The average duration of gestation at the time of operation was 14 weeks. The operation was mostl per formed between the 4th and the 31th weeks of pregnanc as described in Table II. On the average the patients we kept in hospital for 7 days after the operation Proge terone, isoxsuprine and ethyl alcohol ere given befo and after the operation to prevent premature contractio of the uterus.

The operation was mostly performed by using a 5 m wide Ethicon Mersilene Band, × BP _, RS—. Aft making a short anterior incision and freeing the bladd from the cervix the band was tightly ligated around th cervix deep to the epithelium of vaginal fornices an near the level of the internal os. The band as remove at the onset of labour or if rupture of the foetal mem branes or symptoms of inevitable miscarriag. occurred.

To evaluate the benefit of the operation the final suc cess rate and the previous foetal salvage rate ere ca culated from the operation series and from a random selected series of normal pregnant women attending th clinic. The ratio of the final success and the previo foetal salvage rates was determined. This ratio as calle foetal salvage ratio in this paper A term "th. amount benefit rate was calculated. This was the percentage re maining after the benefit rate (final success rate minu previous foetal salvage rate) of the control series had been subtracted from the benefit rate of the operatio series. Legal abortions were excluded when calculating previous foetal salvage rates in either of the groups.

RESULTS

The average duration of the pregnancies with the cervical cerclage was 35 weeks, and the average length of the pregnancies after the operation was 21 weeks.

The final success rate after the operations was 83 2 (104 living infants and _1 which were lost). The abortion rate was 13 6 . (17 cases). Premature deliveries with loss of the child were

Table II *Relation of pregnancy week at the time of operation to the foetal salvage ratio (final success rate per previous foetal salvage rate)*

Pregnancy week t operation	N	Final uccess rate ( )	Previous foetal salv ge rate ( )	Foetal salvage ratio
4–7	1	100 0	75 0	1.3
8–11	6	76 9	_5 0	3.1
1 15	49	79 6	3 1	2.5
16–19	31	87 1	26 5	3 3
20–_3	7	85 7	4_9	0
4–27	5	100 0	54 4	1 8
28–31	1	100 0	0 0	
Operation bef re pregnancy	1	100 0	11 1	9.0

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RADICAL SURGERY AND RADIOTHERAPY IN THE MANAGEMENT OF 173 CASES OF CARCINOMA OF CERVIX UTERI

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Abstract. A total of 173 surgically treated cases of carcinoma of the cervix uteri are presented. Wertheim's radical hysterectomy with lymphadenectomy was performed on 137 patients. 158 patients were also given radiotherapy. The 5 year cure rate for the series as a whole was 82.1%. The operative mortality was 0.6. Fistulae of various types were encountered in 9.8. During the same period, 467 patients with carcinoma of the uterine cervix were treated by radiotherapy. The 5 year cure rate was distinctly better for the surgically-treated patients with Stage I carcinoma and slightly better than those with Stage II carcinoma. The incidence of fistula is the same in both groups. Complications of different grades were more numerous on the whole in the cases treated by radiotherapy alone.

The role of surgery in carcinoma of the cervix uteri has grown steadily in the last decade. In addition to the development of anaesthetic methods, improved sterility, advances in operative techniques, etc., this is due to the fact that patients come for treatment at an earlier stage and thus the possibility of successful operative therapy increases. To ensure good results, surgery is supplemented by radiotherapy in the majority of the cases.

Twenty-four radical operations for carcinoma of the cervix uteri were performed in the years 1926–30 at Departments I and II of Obstetrics and Gynaecology, University Central Hospital, Helsinki (Chydenius, 1936). The average annual number of radical operations was 11 from 1931–40 (Turtola, 1947), 12 from 1941–5 (Purhonen & Turtola, 1958) and 14 from 1953–58 (Turunen & Vara, 1964) in the same clinic. Our series of surgically-treated cases of carcinoma of the uterine cervix dates back to 1959–63 when the average number of radical operations per annum was 77. The prognosis has improved with the increase in the frequency of operative therapy both for the total series and for the cases managed by surgery alone (Table I).

MATERIAL AND RESULTS

A total of 640 patients with carcinoma of the cervix uteri were treated at Departments I and II of Obstetrics and Gynaecology, University Central Hospital, Helsinki in 1959–63, and 173 (27%) of them were operated on. Wertheim's radical hysterectomy with lymphadenectomy was performed in 137 cases. Table II shows the distribution of the patients by type of operation and clinical stage of the carcinoma. The patients in the group "Others" had subtotal hysterectomy and bilateral salpingo-oophorectomy in lieu of the planned Wertheim operation as carcinoma was detected unexpectedly also in the ovaries and peritoneum.

Table III shows the overall therapy (primary carcinoma therapy) administered to 173 patients. Radiotherapy was given to 158 patients. In only 15 cases was the treatment confined to surgery alone. Eighty-three patients received preoperative Ra therapy. The average total dosage of radium was about 2 000–2 500 mg eq/hours, of which the vaginal dose was about 1 200–1 500 mg eq hours and the cervical dose about 800–1 000 mg eq/hours. The average interval between Ra therapy and operation was 2 weeks. External radiotherapy with Röntgen (Müller convergent moving apparatus) was begun 4 weeks after surgery. In cases of Stage I a deep dose of 3 000–4 000 R was given to each parametrium, and in cases of Stage II, one of 4 000–4 500 R. External radiotherapy alone was given to 75 patients, all of them postoperatively.

The 5 year cure rate for the surgically-treated group as a whole was 82.1% and for the patients who underwent Wertheim radical surgery 81% (Table IV). For carcinomata of Stage I the overall 5 year cure rate was 88% and for the patients undergoing Wertheim operation, 85%.

Carcinoma was established in the regional lymph nodes in 18 (13%) of the 137 patients treated by the Wert-

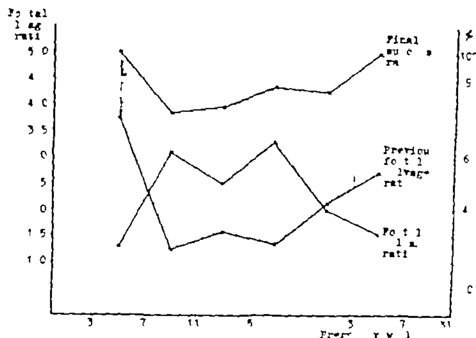


Fig 1 Demonstration of the relationship of the foetal salvage ratio to the *final* success rat and the previous foetal salvage rate after operation at different eeks of pregnancy

same hospital should also be considered. This ef fect is included in the minimum benefit rate, which is not greatly affected by unnecessary oper ations. However the foetal salvage ratio tends to be more sensitive an indicator if there are un necessary operations. Still better as an indicator of needless operations, is the number which results when the foetal salvage ratio of the control series is subtracted from the respective ratio of the operation series. This number should be 0 or less, if all the operations were made without cervical incompetence.

REFERENCES

1 Benson, R. C & Durfee R. B.. Transabdominal cer vico-uterine cerclage during pregnancy for the treat ment of cervical incompetency Obstet Gynec 5 145 1965

– Danforth, D N Cervical incompetency as cause f spontaneous abortion. Clin Obstet Gynec 45 1959

3 Floyd, W S. Cervical dilatation in the mid trimester of pregnancy Obstet Gynec *18* 380 1961

4 Lash, A. F & Lash, S. R. Habitual abortion: the in competent internal os of the cerv x. Amer J Obstet Gynec *59* 68, 1950.

5 Mann, E. C M Laren, W D & Hart, D B The physiology and clinical significance f the uterine isthmus. Amer J Obstet Gynec *81* 709 1961

6. McDonald, I. A.. Suture of the cervix for inevitable miscarriage. J Obstet Gynaec Brit Emp *64* 346, 1957

7 Palmer R. & Lacomme M La béance de l'orifice interne cause d'avortements à répétition Une ob servation de déchirure cervico-isthmique réparée chirurgicalement, avec gestation à terme consécutive. Bull Ass Gynéc Obstét Franc *47* 905 1948

8 Shirodkar V N A new method of operative treat ment for habitual abortion in the second trimester of pregnancy Antiseptic 5 299 1955

9 Strassmann, E. O The Strassmann operation for double uterus. a fifty year experience Obstet Gynec *10* 701 1957

10 Szendi, B Mit dem totalen äusseren Muttermund- erschluss (nach Szendi) gewonnene Erfahrungen und Ergebnisse in der Verhütung der habituellen Abortus und Frühgeburten Zentralbl Gynäk *86* 1363, 1964.

11 Wertheim, E Die erweiterte abdominale Oper tion bei Carcinoma Colli Uteri. Urban & Schw rzenberg. Berlin, 1911

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Stage I *b* receive Ra therapy preoperatively and external radiotherapy using the supervoltage technique, postoperatively. Especially more effective external radiotherapy can be expected to improve the prognosis in the future. The results will probably also benefit from the steady increase in the incidence of early stages in the material from our clinic. This is apparent in the series presented in Table 1 (in greater detail, Nieminen & Pöllänen, 1970) and it also appears from the material collected by Timonen & Nieminen (1970) from later years.

The 5 year cure rate for the total series was of the same magnitude as in other surgically-treated series reported in the literature (Welch, 1961 Christensen et al., 1964 Navratil, 1965 Masterson, 1967). Patients with carcinoma of Stage I treated surgically at our clinic had a distinctly better prognosis than those treated by radiotherapy alone, 88 and 70% respectively whereas the difference was smaller 48 and 44% in Stages II *a* and II *b* (Nieminen & Pöllänen, 1970).

Only 22% of the patients with glandular metastases were alive after 5 years. The 5 year cure rate for these patients in Stage I *b* was 25%. Better results have been reported in the literature, e.g. by Masterson (1967) 42% and Kolstad (1968) 50%.

The incidence of complications in our material was the same as in other series reported in the literature. According to Kjellgren (1967), for instance, fistulae were encountered in 10–15% of surgically-treated cases. In our series, fistulae were established in 9.8% in all. The post-operative incidence of radiologically-diagnosed changes in the urinary tract is also high, but they are mostly reversible. This observation was made also from study of cases from our clinic by Timonen (1967). It is important that the changes that occur in the urinary tracts are followed up and that prophylactic treatment against urinary tract infections is maintained after initial therapy. Infections encountered must be treated carefully. The incidence of fistulae in patients with carcinoma of the cervix uteri treated by radiotherapy alone during the corresponding period was the same, 9.7% (Nieminen & Pöllänen, 1970).

The *mortality during* therapy was very low 0.6% compared with the figures reported in the literature.

REFERENCES

Christensen, A., Lange, P. & Nielsen, E. Acta Obstet Gynec Scand *43* suppl. 2 59 1964.

Chydenius, J. J. Finska läk sällsk handl 9: 755, 1936.

Kjellgren, O. Gynekologisk cancer Klinik och terapi. Almqvist & Wiksell, Stockholm, 1967

Kolstad, P. Personal communication, 1968.

Masterson, J. G. Clin Obstet Gynec *10*: 922, 1967

Nieminen, U. & Pöllänen, L. Acta Obstet Gynec Scand. To be published 1970.

Navratil, E. Clin Obstet Gynec *8* 676, 1965

Parkkinen, T. & Turiola, V. Ann Chir Gynaec Fenn 47 suppl. *81* 1958.

Timonen, S. Ann Chir Gynaec Fenn 56 361 1967

Timonen, S. & Nieminen, U.: Duodecim. To be published 1970.

Turiola, V. Acta Obstet Gynec Scand *4* 27 1947

Turunen, A. & Vara, P. Acta Obstet Gynec Scand 7 suppl. 7 62, 1964.

Welch, J. S., Pratt, J. H. & Symmonds, R. E.: Amer J Obst Gynec *81* 978, 1961.

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Table I *Series of cases of carcinoma of the cervix uteri collected from the Women's Clinic (Stage I–V)*

The material included 6 cases with carcinoma of the corporis et cervicis uteri

	Treated by irradiation		Treated by irradiation + surgery		Total 5 year cure rate (%)
	No of cases	5 year cure rate (%)	No of cases	5 year cure rate (%)	
Chydenius 1926–30	201	20.9	25	68.0	26.1
Turtola 1931–40	821	23 7	110	61 8	23.7
Putkinen & Turtola 1941 52	979	40.8	143	69.2	40 8
Turunen & Vara 1953–58	653	44 1	88	81.8	44 1
Nieminen & Pöllänen 1959–63	467	39 1	173	82.1	50.2

Table II *Numbers and types of operations in the different stages*

		Type of operation			
Stage	Total	Wertheim	Hysterectomy (abdominal)	Hysterectomy (vaginal)	Others
I*a*	32	15	16	1	—
I*b*	114	102	9	2	1
II*a*	17	14	2	1	—
II*b*	9	5	4	—	—
IV	1	1	—	—	—
I–IV	173	137	31	4	1

heim operation. The cases were distributed as follow c cording to the clinical stage

Stage	No. of cases	No. alive after 5 years	
I*b*	12	3	25
II*a*	4	1	
II*b*	1	—	
IV	1	—	
Total	18	4	22

Follow-up examinations revealed complications in the urinary tract in 122 patients, mostly infection (8? cases). These 1— cases included the 69 patients who displayed urinary tract changes on urography (hydroureter and or hydronephrosis) and 1 incontinent cases. Fourteen of the patients suffering from incontinence were cured by treatment f the infection. These 1— patients also included the 17 who developed a fistula after the treatment. The fistulae were distributed in the genital tract in the following w y

Ureterovaginal fistula	11
Vesicovaginal fistula	
Colovaginal fistula	2
Rectovaginal fistula	1
Vesicorectovaginal fistula	1
	17 (9.8%)

Thirty-three patients complained of arious intestinal disorders at follow-up. The commonest condition was irritation of the intestinal mucosa caused by radiotherapy This figure includes the two rectovaginal fistulae mentioned above Only 6 patients were left ith permanent disorders.

Only 1 patient (0.6%) died in the course of therapy She developed an abscess in the region of the left parametrium, followed by high fever and death eeks postoperatively

DISCUSSION

Uniform treatment of carcinoma of the uterine cervix was still not established at our clinic in 1959–63 This is shown by the diverse forms of treatment especially for carcinomas of Stage I *Radiotherapy alone is no longer* used in our clinic for carcinomas of Stage I*a*. All cases of

Table III *Primary therapeutic methods*

Stage	Surgery	Radium + Surgery	Surgery + X-ray	Radium + Surgery + X-ray	Total
I*a*	9	2	18	3	32
I*b*	4	3	48	59	114
II*a*		1	4	10	17
II*b*	—	—	4	5	9
IV	—	—	1	—	1
I–IV	15	6	75	77	173

Table IV *Situation five years after the institution of therapy*

	Whole series		Treated by Wertheim operation	
Stage	Total	Alive	Total	Alive
I*a*	32	30 } (88)	15	13 } (85 .)
I*b*	114	99 }	102	87 }
II*a*	17	9	14	7
II*b*	9	4	5	4
IV	1		1	—
I IV	173	142 (82 1)	137	111 (81)

Stage I *b* receive Ra therapy preoperatively and external radiotherapy using the supervoltage technique, postoperatively. Especially more effective external radiotherapy can be expected to improve the prognosis in the future. The results will probably also benefit from the steady increase in the incidence of early stages in the material from our clinic. This is apparent in the series presented in Table I (in greater detail, Nieminen & Pöllänen, 1970) and it also appears from the material collected by Timonen & Nieminen (1970) from later years.

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The mortality during therapy was very low, 0.6%, compared with the figures reported in the literature.

REFERENCES

Christensen, A., Lange, P. & Nielsen, E.: Acta Obstet Gynec Scand *43* suppl. *2* 59 1964.

Clydenius, J. J.: Finska läk sällsk handl *9* 755 1936.

Kjellgren, O.: Gynekologisk cancer. Klinik och terapi. Almqvist & Wiksell, Stockholm, 1967.

Kolstad, P.: Personal communication, 1968.

Masterson, J. G.: Clin Obstet Gynec *10* 922, 1967.

Nieminen, U. & Pöllänen, L.: Acta Obstet Gynec Scand. To be published 1970.

Navratil, E.: Clin Obstet Gynec *8* 676, 1965.

Pakarinen, T. & Tortola, V.: Ann Chir Gynaec Fenn *47* suppl. *81* 1958.

Timonen, S.: Ann Chir Gynaec Fenn *56* 361 1967.

Timonen, S. & Nieminen, U.: Duodecim. To be published 1970.

Tortola, V.: Acta Obstet Gynec Scand *4* 27 1947.

Turunen, A. & Vara, P.: Acta Obstet Gynec Scand *7* suppl. *7* 62, 1964.

Welch, J. S., Pratt, J. H. & Symmonds, R. E.: Amer J Obstet Gynec *81* 978, 1961.

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EXPERIMENTAL STUDY OF A NEW COMBINATION OF SURGERY AND RADIOTHERAPY FOR TREATMENT OF CARCINOMA OF CERVIX UTERI

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Abstract. An experimental series of 12 patients consisting of 10 cases with carcinoma of the cervix uteri and 2 with carcinoma of the corpus uteri were treated by a new method combining surgery and radiotherapy. The purpose was to study the safety of the method, in other words, whether its use could be continued. It had been found to be safe theoretically. During the follow-up period of 3 years the incidence of complications due to the new therapy was not even on the scale common with the conventional combined method of treatment.

Key words: carcinoma of the cervix uteri

At the First Department of Obstetrics and Gynaecology, University Central Hospital, Helsinki, we began at the end of 1966 to use a new combination of surgery and radiotherapy for the treatment of carcinoma of the cervix uteri (Nieminen, 1968). This method involves the administration during Wertheim's operation, of contact therapy to the region of both lateral parametria by means of a special isotope applicator in which caesium is the source of radiation. The mean energy of the caesium unit is 0.662 MeV and the radiation energy consequently lies between that of ^{60}Co and 250 kV roentgen radiation. Unnérus and his co-workers (1964) developed this automatic applicator unit for intracavitary radiotherapy in our clinic.

The method aims at replacing a part of the external radiotherapy which must be administered postoperatively to the parametria through other organs. It is impossible in the latter treatment to avoid irradiation damage to these adjacent organs as well. The extent of the damage depends on the amount of radiation. It is possible during surgery to move organs from the area to be irradiated, thus reducing the amount of radiation received by them. The use of the isotope applicator also permits more thorough irradiation of the area under treatment than does external therapy.

I have found no mention in the literature of the use of the after-loading apparatus in the management of carcinoma of the cervix uteri in conjunction with radical surgery. Guseo (1959) and Shinagawa (1963) reported that at the time of a radical operation (for cervical cancer) they placed radium needles along the line of the lymphatics from the level of the lower pole of the kidneys to the vaginal region. The radium needles were removed after 4–5 days. This ensured the destruction of small metastases that might have been left in the lymphatics despite radical lymphadenectomy.

METHOD AND MATERIAL

The method has already been described in detail (Nieminen, 1968). As the method seems not to have been employed earlier, it was felt that a small initial series was necessary to establish that it was safe. The mode of treatment had been checked theoretically and calculated to be safe.

Urography was performed and the renal function examined in addition to other routine preoperative studies prior to the institution of therapy. Urography was repeated and the renal function re-examined postoperatively before external radiotherapy was commenced, then 2 months and 1 year after the completion of radiotherapy and again whenever necessary later.

All the patients were given a single, preoperative radium treatment of 2 000–3 000 R to the

tumour area a week before Wertheim's operation The operation with lymphadenectomy was performed 1–4 weeks after radium therapy depending on the patient's condition The last 6 patients were operated on within a week of the radium therapy

Caesium application was given for 5–10 min to the region of both parametria during the operation. The energy dose was that mentioned previously

The total treatment time, taking both sides into consideration, was 10–20 min The amount of radiation during this time to the region of each parametrium was around 500–1 000 rad, i.e. the total dosage was 1 000–2 000 rad.

External radiotherapy was commenced 1–4 weeks postoperatively In the last 6 cases to be treated external therapy was begun a week after the operation It was administered as moving field Röntgen therapy

Röntgen therapy was given so that the depth dose to the parametria, including the preoperative radium and caesium therapy was about 4 000 rad (at point B) Ten patients with carcinoma of the uterine cervix were treated by this method in the course of 4 months: eight of them were of Stage I *b* and two of Stage II *a*. In addition two carcinomas of the corpus uteri of Stage II were treated. In the first 6 cases the caesium treatment time during the operation was from 5 to 7.5 min on each side (total treatment time was 10–15 min) In the last 6 cases the treatment time for each side was 10 min (total treatment time 20 min)

RESULTS

As the principal aim of the method in question is to reduce damage caused by radiotherapy to healthy organs, the results can be reviewed 3 years after therapy Most of the lesions produced by radiotherapy originate and disappear within this time.

Four patients developed unilateral hydroureter and or hydronephrosis after surgery and in 2 of these cases before the institution of Röntgen therapy One of these patients also developed an ipsilateral lymphocyst. The function of the kidneys and ureters returned to normal during the follow up period in all cases.

One of the patients developed rectal symptoms approximately a year after surgery A barium enema revealed no changes, but sigmoido-scopy established mucosal irritation in the rectal region. The symptoms disappeared in 3 months. None of the other patients had intestinal complaints.

Difficulties with micturition appeared in 1 case 3 years after therapy Both urography and cystoscopy showed no abnormality The urinary symptoms cleared with the disappearance of bacteriuria.

The third patient treated began to feel ill during preoperative radium therapy and it had to be discontinued. She made a good recovery and was completely asymptomatic at the time of her operation 4 weeks later During the operation she was given caesium therapy to both parametria for 7.5 min. Roentgen therapy was instituted 4 weeks postoperatively but had to be discontinued as the patient was not feeling well. She died 7 months after the start of therapy Autopsy revealed the immediate cause of death to have been severe acute hepatic necrosis. The operative area and the adjacent organs were intact, i.e. there was no appreciable radiation reaction. The tumor dose from the preoperative radium treatment was 2 000 rad from caesium therapy the dose to each the parametria was 750 rad, and from Röntgen therapy a depth dose of 2 000 rad was given to each side

DISCUSSION

The incidence of ureteric stricture (hydroureters and hydronephroses) in patients given combined operative and radiotherapy in different series varies from 1–12% These complications occurred in 14 of the 43 patients (after 1–3 years, 4 of the 43 patients) in the series treated with surgery and radiation (the usual method) at our clinic which Timonen (1967) described. As these complications are encountered to a considerably smaller extent in cases treated with radiotherapy alone (according to Timonen 2 of his 45 patients) it is probable that they arise from the operation In the present series, 4 out of 1 patients had a temporary hydroureter and or hydronephrosis (finally 0) The ratio is the same as in the series treated with conventional combined therapy As is well known these changes are mostly reversible

Only 1 patient had urinary complaints, due to

urinary tract infection. No radiological changes were established in this patient's urinary system in any phase. Urinary complaints are the commonest complications of both surgery and radiotherapy

Intestinal complaints occurred in 1 patient only In the material reviewed by Nieminen & Pöllänen (1970) they were present in 19% of the patients managed by surgery plus radiation and in 34% of those treated with radiotherapy

The death of the third patient treated cannot be attributed, at least not directly to the radiotherapy The post-mortem examination suggested that the result would have been the same even if the patient had been treated by the conventional procedure, in which the surgical trauma would have been the same and postoperative radiotherapy certainly the same.

The present series is too small to warrant further conclusions, but it does show that the method is safe. Only a larger series and longer follow-up period will reveal whether the method can achieve the advantages it possesses in theory

REFERENCES

Gauss, A., Krebsforschung und Krebsbekämpfung, Band III, p. 48. Urban & Schwarzenberg, München, 1959

Nieminen, U Acta Obst Gynec Scand 47 52, 1968

Nieminen, U & Pöllänen, L. Acta Obst Gynec Scand. To be published 1970.

Shinagawa, S J Japanese Obst Gynec Soc 10 125 1963.

Timonen, S. Ann Chir Gynaec Fenn 56 361, 1967

Unnérus, C.-E., Nieminen, T Rekonen, A. & Vauramo, E. Ann Chir Gynaec Fenn 53 480, 1964.

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GAMMA CAMERA EXAMINATION OF PREGNANT UTERUS AND PLACENTAL PERFUSION

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Abstract. Radioactive ^{99m}Tc (300 μCi) tracer and gamma camera were used to study placental function between the 34th and 40th weeks of pregnancy in 10 women with normal pregnancy, 34 with mild and two with severe pre-eclampsia. The placenta was first localised by the Doppler method and then the gamma camera was turned at right angles to the site. After the injection the radioactivity over the placenta was counted and a series of radiographs was made at intervals of 30 sec for up to 12 min. The two values correlated. When the material was grouped according to the week of pregnancy, perfusion was fastest in the 34th week (3.1 ± 0.87 min) and slowest in the 40th week (5.5 ± 1.27 min). The difference is significant. There was no significant difference when the material was divided into groups on the basis of normal and toxaemic pregnancies.

Localisation of the placenta with radioactive isotopes has already achieved a prominent role in routine use at women's hospitals. The first studies involved the intravenous injection of RISA ^{131}I and measurement of the radioactivity over the uterus (Hibbard, 1961; Laakso et al., 1964). The tracer used today is ^{99m}Tc, either as sterile sodium pertechnetate solution or bound with albumin (McAfee et al., 1964; Tautz, 1966).

Levine et al. (1967) used radioactive ^{99m}Tc pertechnetate solution to localise the placenta and with a gamma camera took a fast series of radiographs which showed that the level of radioactivity reached its maximum in about 5 min. The amount of radiation in the fetus with a dose of 300 μCi was 5 mRad.

The purpose of our study was to find out whether the radioactive tracer reaches maximum activity at different times in different parturient groups and, thus, whether it is possible to use this as information about placental function.

MATERIAL AND METHODS

The series consisted of 10 cases of normal pregnancy, 34 of mild pre-eclampsia and 2 of severe pre-eclampsia. The examinations were performed between the 34th and 40th weeks of pregnancy.

The placenta was first localised by the Doppler method (Doptone, Smith Kline Instr. Co.). If the placenta was found to be lying anteriorly or on the lateral uterine wall, the investigation was continued. The latter cases were given potassium perchlorate for 2 days in order to block both the maternal and the fetal thyroid gland. For the examination proper the gamma camera (Nuclear Chicago, PHo/Gamma III) was directed perpendicularly to the probable location of the placenta. The patient was given an intravenous injection of 300 μCi of ^{99m}T -pertechnetate. Exposures were made and the radioactivity counted at intervals of 30 sec. This was continued up to 12 min from the injection. The peak radioactivity was charted from the results. Different observers studied the radiographic series and the readings and the results were then combined.

RESULTS

The time after injection of maximum placental radioactivity obtained from the radiographic series and from the direct counter were correlated (Fig. 1).

According to the radiographic series, the maximum time in normal pregnancies was 4.8 ± 0.79 min, and according to the counter 4.9 ± 1.08 min. The times for the group with mild pre-eclampsia were 4.5 ± 0.91 and 4.2 ± 1.22 min, respectively. As there were only 2 cases with severe pre-eclampsia they were not considered separately nor included in the above groups. No significant difference was established between the normal group and the pre-eclampsia groups (Table 1).

-mature pregnancies, Jansson (1969) in- ^{133}Xe into the uterine myometrium in the on the side of placenta. The ^{133}Xe clear the myometrium was maximal in the 34th f pregnancy and then decreased towards ulated date of delivery results correlated with the urinary oestriol rations. Our results concur with these find- owever the studies cited above concerned d portion of the uterus or placenta and low varies considerably depending on the men (Greiss & Anderson, 1968). Our measurement comprised the placenta as , the uterus, fetus and amniotic fluid. The give an overall idea of the variations in low in this area. The readings of radio- in all the groups reached about 90 % maximum in 2–3 min and began to de- about 10–12 min after the injection. This terval is the most suitable if the objective ely to localise the placenta. Rosenthal's optimum with the same method was 8 min. ferences were established between the nor d toxaemic pregnancy groups. Nor was ny such difference between normal preg- and toxaemias in the groups distributed ng to the week of pregnancy. On the hand, when the material was distributed by the week of pregnancy the findings with the results reported in the literature her uterine or placental blood flow. Per is decreased towards the end of preg- This finding is physiological and the two ls of examination used here can probably arded as useful indicators of uterine and tal perfusion.

REFERENCES

N Rauramo, L. & Pekonen, T. Amer J Obstet ec 79 86 1960

, J C & Veall, N. J Obstet Gynaec Brit Emp 147 1953

H Browne J & Dowery D Lancet II 369 1963.

F & Anderson, S. Clin Obstet Gynec 11 96, 8

, B M Obstet Gynec 62 481, 1961.

, I Acta Obstet Gynec Scand 48 302, 1969

. I Relander, A. & Holmstrom, T Duodecim 934 1964

. D Fish, M., Pollycove, M. & Kharafgan, M ucl Med 8 773 1967

McAfee, J Stern, H., Fueger G., Baggish, M., Holtzman, G. & Zolle, L. J Nucl Med 5 936, 1964

Moore, P T & Myerscough, P Obst Gynaec Brit Emp 64 207 1957

Rosenthal, L. Canad Med Ass J 97 212, 1967

Tautz, M Nucl Med 5 272, 1966.

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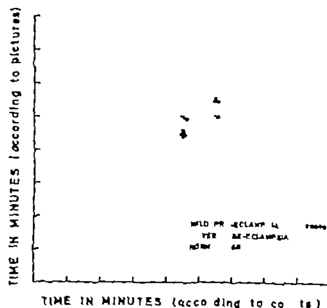


Fig 1 Time in minutes fo each case in which maximum radioactivity was reached according to the counts (y) and the radiographic series ( )

As the readings from the counter are the more objective standard of the two methods they were used in the analysis of the material.

When the cases were distributed solely according to the week of pregnancy (Table I) maximum uptake in the 34th week was $3\,1 \pm 0\,87$ mm, in the 36th week $4\,0 \pm 0\,82$ mm, in the 38th week $4\,5 \pm 1\,10$ and in the 40th week 5.5 ± 1.27 min. The difference was significant only between the groups in the 34th and 40th weeks of pregnancy ($0\,0025 > p > 0\,0005$)

DISCUSSION

Uterine blood flow has been studied by many dif ferent methods. The electromagnetic flowmeter used by Assali et al (1960) measures the blood flow in one uterine artery Browne & Veall (1953) used radioactive ^{24}Na by injecting it directly into the uterine wall and observed that the biological half-life of the substance was longer in an abnormal than in a normal pregnancy The same tracer and method were used by Moore & Myerscough (1957) who found no correlation between the clearance values and degrees of toxaemia. Dixon and co-workers (1963) employed radioactive ^{24}Na for the local measurement of choriodecidual flow and stated the biological half-life of the substance to be 20.45 sec in normal pregnancy 133.5 sec in pre-eclampsia and 43 75 sec

Table 1 Material distributed according to the week of pregnancy

Week of pregnancy	Subj No	Maximal uptake according to: counts	pictures
34	3	3.0 min	3.0 min
	1	4.5	4.5
	15[a]	4.0	4.0
	22	4 0	4.5
	33	2.5	3.0
	34	2.0	2.5
	35[b]	3.0	4 5
	45	2.0	4.0
	8	M 3 1 S.E. ± 0.87	M 3 6 S.E. ± 0.66
36	4	5.0	5 0
	5	3 0	3.0
	10	4.5	4.5
	13	4.5	4.5
	19	4.5	5 0
	40	3.0	3.5
	56	3.5	3.5
	7	M 4.0 S.E. ± 0.82	M 4 2 S E. ± 0.80
38	2	4.5	5.0
	11	5 0	5 0
	14[a]	4.5	5.0
	16	6.0	6.0
	17	5.5	5.5
	20[a]	6 0	5 0
	23	3.0	3.5
	26	[illegible]5	3.5
	28	5.5	4.5
	29	4 0	5.0
	30	3.0	[illegible]5
	32	4 0	4.5
	37	4.5	4.5
	38	4 0	3 5
	39	6 0	4.5
	41	3.0	4 0
	42	4.5	4 5
	43	4.5	4 0
	44	5.5	5.0
	46	3.5	4 0
	47	5 5	5.0
	21	M 4.5 S E. ± 1 10	M 4.5 S E. ± 0.79
40	1	6.5	5 5
	6[a]	5 5	5.5
	7[b]	8 5	7.0
	8[a]	5 5	5 0
	18[a]	4 0	4 0
	1	5 5	5.5
	24	5 0	4.5
	25[a]	4 5	4 5
	27	4 5	5 0
	31	5 5	4 5
	10	M 5.5 S.E. ± 1 27	M 5 1 S E ± 0.71

Normal pregnancy
[b] Severe pre-eclampsia

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EFFECT OF ETHYL ALCOHOL ON URINARY EXCRETION OF NORADRENALINE AND ADRENALINE IN PATIENTS WITH THREATENED PREMATURE DELIVERY

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Abstract. The effect of oral intake of alcohol on noradrenaline and adrenaline excretion in 24 hour urine was studied in 18 pregnant women admitted to hospital in the second half of pregnancy for premature onset of uterine contractions. In control specimens of 24 hour urine, the mean excretion of noradrenaline was 29.6 µg per 24 hours. After ethyl alcohol administration, the excretion in the first 24 hours rose to 46.0 µg and in the second 24 hour period to 37.6 µg. The mean excretion of adrenaline in control specimens was 7.4 µg per 24 hours. In the first 24 hours of ethyl alcohol treatment it averaged [illegible]3 and in the second 24 hour period 7.6 µg per 24 hours.

The inhibition of premature uterine contractions is a problem continually met with in obstetric practice, and new drugs are being developed to solve it. In recent years, ethyl alcohol has been found to inhibit uterine contractions both in laboratory animals and man (Fuchs & Wagner 1963, Fuchs, 1965, 1966, 1967, Luukkainen et al. 1967). From her experiments, A. R. Fuchs came to the conclusion that the inhibiting action of ethyl alcohol on uterine contractions was due to reduced secretion of oxytocin from the posterior lobe of the hypophysis, although no direct proof was obtainable, since the quantities of oxytocin are infinitely small and difficult to determine.

Adrenaline is a drug which has long been used to suppress premature contractions of the uterus. It has been found to reduce significantly both the frequency and intensity of the contractions. Large quantities of ethyl alcohol have been found to increase the release of adrenaline from the adrenal medulla in dogs (Klingman & Goodall, 1957). Increase in the urinary adrenaline under the influence of ethyl alcohol has also been demonstrated in man (Perman, 1958) whereas Anton (1965) found that the excretion of noradrenaline increased more than of adrenaline.

The purpose of the present study was to examine the effect of oral administration of ethyl alcohol on the urinary excretions of noradrenaline and adrenaline in pregnant women admitted to hospital because of premature uterine contractions in the second half of pregnancy.

MATERIAL AND METHOD

The series consisted of 18 pregnant women admitted to the Department of Obstetrics and Gynaecology, University of Oulu, for premature labour contractions. At the time of admission, they were between the 26th and 38th weeks of pregnancy. The membranes had ruptured by the time of admission in 2 patients, Shirodkar's operation had been performed on a third in the 20th week of pregnancy, while a fourth had mild pre-eclampsia. None of the 18 patients showed any signs of urinary tract infection.

Immediately on admission the patients were confined to bed, and treatment was started with cognac containing 34% ethyl alcohol. The dosage was 90 ml at 6 hour intervals. No other drugs, apart from iron compounds, were given. The administration of alcohol continued until contractions ceased. From the beginning of alcohol therapy 24 hour urine samples were collected twice for most patients, three times for some. After the contractions had ceased the administration of ethyl alcohol was interrupted for 24 hours, after which a control 24 hour urine sample was collected. While the collection went on the patients were given no drugs at all. Three patients were excluded from the series, since their contractions started again during the control period and ethyl alcohol therapy had to be re-instituted. A few determinations failed owing to confusion in the collection of urine.

Noradrenaline and adrenaline were determined from urine samples collected in the presence of sodium metabisulphite according to the principle described by

DISCUSSION

In the present study the suppressive action of ethyl alcohol on premature contractions of the uterus was found to be good. This finding agrees with earlier reports (Fuchs, 1965 Luukkainen et al., 1967). Ethyl alcohol was found to increase the excretion of both noradrenaline and adrenaline into the urine. The increased urinary excretion of these substances is usually attributed to their increased release from the adrenal medulla. Ethyl alcohol has been found, however to have an inhibitory effect on the mono-amino oxidase (Rosenfeld, 1960), which plays an important role in the metabolism of catecholamines. It is therefore possible that increased urinary excretion of noradrenaline and adrenaline during ethyl alcohol therapy might be a result of the inhibition of this enzyme. When Anton (1965) found that ethyl alcohol administration increased most significantly the urinary excretion of noradrenaline, normetanephrine and metanephrine, he attributed some of it to the inhibition of mono-amino oxidase.

The urinary excretion of noradrenaline increased more than that of adrenaline. Noradrenaline does not, however suppress uterine contractions, on the contrary it increases the basic tonus of the uterus, and raises the frequency and intensity of the contractions (Cibils et al., 196). Hence the decrease in contractions due to the action of ethyl alcohol cannot be explained on the basis of increased release of noradrenaline.

Increase in adrenaline excretion under the action of ethyl alcohol was less pronounced. The effect of adrenaline on pregnant uterus in the last few weeks of pregnancy is inhibitory After adrenaline administration, the frequency and intensity of uterine contractions decrease (Pose et al 1962). Its clinical use is, however limited by the short duration of its action, the rebound effect, and the cardiovascular side effects.

The effects of both noradrenaline and adrenaline on the myometrium can be understood on the basis of the so-called receptor theory The former substance stimulating alpha receptors, increases contractions. The action of noradrenaline on myometrium can be prevented by substances blocking this type of receptor, e.g. by phentolamine (Wansbrough et al., 1968). The relaxing effect of adrenaline on the uterus can probably be explained from the predominant position of beta receptors in the uterus during the last few weeks of pregnancy Adrenaline stimulates, in fact, both types of receptor Uterine activity can be increased by drugs blocking beta receptors, e.g. propranolol. The distribution of the sympathetic nervous system and its effects on uterine function are still to some extent uncertain. It does not seem probable, however that the changes, recorded in the present study in the quantities of noradrenaline and adrenaline released by the adrenal organism, could explain the reduction in uterine contractions.

In the present study increase in both noradrenaline and adrenaline excretion due to the action of ethyl alcohol was found to be much more pronounced in the first 24 hours than later This may have resulted from the anxiety and fear the premature onset of contractions had produced in the patient. The excretion of both these substances has been found to be increased in conditions of anxiety and fear (Elmadjian et al., 1958 Levi, 1961). On the other hand, the psychic relaxation produced by ethyl alcohol may contribute to reducing the secretion of noradrenaline and adrenaline on the second and third days of treatment. The dilating effect of ethyl alcohol on cutaneous blood vessels may also increase the release of noradrenaline when the vascular contraction it produces elsewhere in the organism inhibits any fall in blood pressure.

REFERENCES

Anton, A H. Clin Pharmacol Ther 6 462 1965

Anton, A. H. & Sayre, D. F J Pharmacol Exp Ther 138. 360, 1962.

Cibils, L. A., Pose, S. V & Zuspan F P Amer J Obstet Gynec 84 307 1962.

Elmadjian, F Hope, J. M. & Lamson, E. T Recent Progr Hormone Res 14 513 1958.

Fuchs, A-R. J Endocrin 35 125 1966.

Fuchs, A-R. & Wagner G., Acta Endocrin 44 593, 1963.

Fuchs, F J Obstet Gynaec Brit Comm 72. 1011 1965.

Fuchs, F Fuchs, A-R., Poblete V F & Risk, A. Amer J Obstet Gynec 99 627 1967.

Khagreen, G L & Goodall, M. J Pharmacol 121 313 1957

Levi, L. Acta endocrin (Kbh) 37 38 1961.

Luukkainen, T Väistö, L & Järvinen, P A. Acta Obst Gynec Scand 46 486, 1967

Persson, E. S Acta Physiol Scand 44 41, 1958

Table I *The effect of ethyl alcohol on the urinary excretion of noradrenaline and adrenaline for 3 days*

	Noradrenaline excretion µg/24 hr				Adrenaline excretion µg/24 hr			
Patient	Control day	1	2	3	Control day	1	2	3
I	14.7	38.9	31.8		8.7	9.4	11.2	
II	34.7	29.0			10.9	11.6		
III	33.3	47.8	74.3		4.8	11.1	5.8	
IV	14.6	16.3	18.0		6.6	7.1	10.7	
V	24.6	27.6	28.1	10.6	8.4	6.5	10.2	8.8
VI	36.5		28.8	25.1	2.0		2.0	1.9
VII	21.6	45.8	15.9		5.7	7.8	2.6	
VIII	30.7	53.1	63.5	36.5	2.6	14.7	5.5	6.5
IX	40.7	84.1	54.6		17.6	16.3	17.9	
X	23.6	119.7	90.7		20.8	7.6	10.4	
XI	42.2		56.6		4.3		4.2	
XII	43.8	28.6	39.9		6.4	5.3		
XIII	16.0	11.6	19.5	5.5	2.9	2.3	2.6	3.8
XIV	13.5	26.5	14.1		10.6	10.3	20.1	
XV	34.6	46.7	26.2		3.4	3.8	1.0	
XVI	36.4	29.9	29.7		4.2	7.6	7.9	
XVII	14.4	16.8	9.3		5.7	2.1	1.9	
XVIII	56.5	55.1		70.9	8.0	25.0		11.1
Mean	29.6	48.0	37.6	29.7	7.4	9.3	7.6	6.4
S.E.M	2.9	3.6	5.9	11.7	1.2	1.4	1.5	1.7
$P <$		0.025	0.15	0.497	0	0.20	0.475	0.45

Anton & Sayre (1962). According to this method, the urine is made acid by adding perchloric acid, noradrenaline and adrenaline are adsorbed selectively into aluminium in an alkaline environment, and elution from aluminium is made by perchloric acid under shaking in a centrifuge tube. Oxidation into a trihydroxy-indole derivative takes place with potassium ferricyanide in alkaline ascorbate solution. Measurements are made with spectrophotofluorimetry at two pH levels using maximum wavelengths of fluorescence to separate noradrenaline and adrenaline.

Student's t-test was used in the statistical treatment. Since individual differences in the excretion of noradrenaline and adrenaline were fairly large, the values for each patient were compared with her own control values.

RESULTS

In 8 of the 18 patients of the series, contractions ceased after 1–5 days of treatment these patients were discharged from hospital and none needed re-admission prior to the calculated date of delivery. In 9 patients contractions re-occurred soon after the administration of ethyl alcohol had been discontinued, and premature delivery occurred 1–3 weeks after admission despite prophylactic treatment. In 1 patient, it was possible to postpone delivery despite recurrent contractions, from the 33rd to the 39th week.

The 24-hourly excretions of noradrenaline and adrenaline of each patient are given in Table I. During the first 24 hours, when the patients were given ethyl alcohol, a distinct increase in noradrenaline excretion was seen to occur as compared with the control values collected later. The mean excretion during the control 24 hours was 29.6 µg and during the first 24 hours of treatment 48.0 µg. The change was statistically significant ($P < 0.025$). During the second 24 hour period the excretion of noradrenaline showed a declining trend (mean excretion maximum 37.6 µg), and the difference against the control values is not significant ($P < 0.15$). A third 24 hour sample was collected from 5 patients only. A declining trend seemed to continue.

The mean excretion of adrenaline during the 24 control hours was 7.4 µg. During the first 24 hours of ethyl alcohol therapy the excretion rose to a mean value of 9.3 µg. The change is not significant statistically ($P < 0.20$). During the second 24 hour period with ethyl alcohol treatment the excretion of adrenaline fell close to the control values (mean excretion 7.6 µg). During the third 24 hour period the declining trend seemed to continue.

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FIBRINOLYTIC SPLIT PRODUCTS IN SERUM AND URINE IN PREGNANCY

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Abstract. Toxaemia and certain other complications of pregnancy appear to be accompanied by deposition of fibrin and microthrombosis in the kidneys, liver and placenta. When broken down these deposits and thrombi produce degradation products or split products. To assess the diagnostic value of determination of split products in serum and urine, 1 001 pregnant women were examined, on a single occasion during the latter part of pregnancy. 99 were found to have split products in the serum in a concentration of up to 3 mg/100 ml and 83.8% of them were found to have some complication, particularly toxaemia, hepatosis and urinary tract infections. No split products could be demonstrated in the urine in any of the women. Determination of fibrinolytic split products in serum is therefore recommended for early detection of complications and as an indicator of the effect of treatment of various complications during pregnancy.

Recently much attention has been directed to the properties of fibrinolytic split products (FSP) and their occurrence in various diseases (2, 6, 7, 11). The most widely used methods for determining split products are the haemagglutination inhibition immunoassay (2, 7) and an immunochemical method devised by Nilsson (11).

FSP occur in the blood in the presence of diseases with associated systemic fibrinolysis, intravascular coagulation with secondary fibrinolysis or local deposition of fibrin with secondary fibrinolysis. Split products have recently been found to occur in small amounts during normal pregnancy (1, 15) and in larger amounts at complicated deliveries (1).

In the present investigation we determined FSP in 1 001 pregnant women to find out, first, whether FSP could be demonstrated in the blood and/or urine of a large series of patients during the latter part of pregnancy and, second, to what extent their occurrence is an indicator of some complication of pregnancy.

MATERIAL AND METHODS

Single venous blood and urine samples were obtained from 1 001 women at routine antenatal examination during the last 2 months of pregnancy. They were examined for split products. After delivery the hospital records were examined for any subsequent complications in the mothers or the infants. A woman was said to have had toxaemia if she had had oedema requiring treatment, proteinuria or increased blood pressure (diastolic > 95). Hepatosis, a fairly common complication of pregnancy in Sweden, characterized by itching and increased serum transaminases (SGOT and SGPT), was distinguished from other types of toxicosis. Urinary tract infection was diagnosed if culture had given bacterial growth on at least 2 occasions. If the blood loss exceeded 800 ml blood post partum, haemorrhage of unknown origin was recorded.

Collection of blood. Blood was collected in tubes containing an inhibitor of fibrinolysis, E-aminocaproic acid (EACA). Serum from these samples was prepared as described by Nilsson (11). The urine was stored at +4°C without addition of EACA.

Determination of split products. Split products were determined by the immunochemical method of Nilsson (11). In this method an antiserum against the D-fraction of the fibrinogen split products is applied to agarose gel. With high voltage electrophoresis, serum (diluted 1/2) or urine (diluted 1/2) migrates into the gel. If FSP are present, they will produce precipitation peaks. The height of such peaks is measured and related to a standard of high molecular weight substances. In the presence of EACA this method did not demonstrate any FSP in serum or urine from healthy control women also in repeated assays.

RESULTS

Split products in a concentration of up to 3 mg/100 ml were found in 99 of the 1 001 women ex

Pose S. V Cabils, L. A. & Zuspan, F P Amer J Obstet Gynec *84* 297 196_.
Rosenfeld, G Proc Soc Exp Biol Med, *103* 144 1960.
Wansbrough, H., Nakanishi, H. & Wood, C.. J Obstet Gynaec Brit Comm *75* 189 1968.

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found FSP in the serum in 99 (9.9%) including 83 (83.8%) with some complication of pregnancy principally toxaemia, hepatosis or urinary tract infection.

Despite intense research the cause of toxaemia of pregnancy is still obscure. Fluorescence (10) and electron microscopic examination (9) of renal biopsy specimens from women with toxaemia of pregnancy has revealed fibrin deposits in glomeruli. Such deposits of fibrin and thrombi probably occur also in the minute vessels in the liver These changes may cause nephropathy and hepatosis, respectively The breakdown of such fibrin deposits may in turn, give rise to split products. McKay & Corey (8) also feel that toxaemia of pregnancy is associated with a slow process of k of fibrin depositions. Recently Wardle & Menon ( ) published data in support of this theory Our finding of FSP in patients developing toxaemia and hepatosis is thus compatible with the presence of a progressive fibrin deposition.

In *urinary tract infections* small fibrin deposits may occur in the kidneys as a result of the inflammatory process. The FSP often found by us may have been due to dissolution of such deposits.

In the case of *Rhesus-immunization*, the immunological reaction was probably the cause of the fibrin deposits (13).

This explanation may also hold for the *allergic conditions* it being believed (13) that all antigen-antibody reactions can cause an intravascular deposition of fibrin.

The cause of the split products in mothers with *infants with jaundice and thrombocytopenia* is unknown There might be similar immunological reactions

But what explanation can be offered for the occurrence of split products in uncomplicated pregnancy Fox (4) and Devi et al. (3) focused attention on the very common occurence of fibrin deposits and intervillous thromboses in the maternal part of the placenta. Such changes may perhaps sometimes be extensive enough to cause fibrinolysis with FSP in demonstrable amount, but not to produce clinical manifestations.

Placental insufficiency may occur in cases of toxaemia with nephropathy and hepatosis. Its course is generally followed clinically by determinations of oestriol in the urine.—In toxaemia of pregnancy there is probably not only deposition of fibrin and microthrombosis in the kidney and liver but also to greater or lesser degree in the placenta with consequent impairment of function.—This opens up interesting approaches in the search for the cause of toxaemia of pregnancy and adequate causal treatment.

Thus, among the 99 pregnant women with split products in the serum, we found clinical disorders in 83 (83.8%). Of the entire series of 1 001 pregnant women clinical disorders were found in 195 In 152 (77.9%) of these 195 the serum contained split products. This indicates an association between split products and clinical disorders and suggests that determination of split products might prove a useful diagnostic tool. It should however be pointed out that each woman was examined only once for such products. It is possible that repeated examinations would have revealed a higher percentage with split products. — We also feel that this determination may be useful for following the course and effect as well as the choice of treatment of these conditions, e.g. whether or not delivery should be induced. An increasing content of split products in the serum in cases of immunization, nephropathy and hepatosis may probably argue for serious progressive disease.

REFERENCES

1 Bonnar J Davidson, J F Pidgeon, C. F McNicol, G. P & Douglas, A S Fibrin degradation products in normal and abnormal pregnancy and parturition. Brit Med J 3 137 1969

2. Das, P C., Allan, A. G. E., Woodfield, G D. & Cash, J D Fibrin degradation products in sera of normal subjects. Brit Med J 4 718, 1967

3. Devi, B., Jennison, R. F & Langley F A Significance of placental pathology in transplacental haemorrhage. J Clin Path 21 322, 1968

4 Fox, H. White infarcts of the placenta. J Obstet Gynaec Brit Cwlth 70 980, 1963

5 Larsson, S. O Hedner U & Nilsson, I. M. Coagulation studies in severe chronic renal insufficiency The 4th International Congress of Nephrology Stockholm, 1969

6 Marder V J Immunologic structure of fibrinogen and its plasmin degradation products: theoretical and clinical considerations. *In* Fibrinogen (ed. K. Laki), Dekker Inc., New York, 1968.

7 Merskey C Kleiner G J & Johnson, A J Quantitative estimation of split products of fibrinogen in human serum, relation to diagnosis and treatment. Blood 28 1 1966.

8 McKay D G & Corey A. E. Cryofibrinogenemia in toxemia of pregnancy Obstet Gynec 23 508 1964.

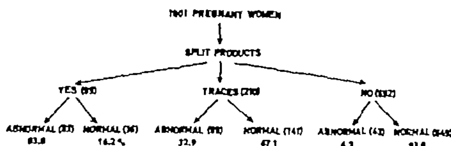


Fig 1 Frequency of fibrinolytic split products in serum and complications of pregnancy in 1 001 pregnant women examined.

amined, traces of such products in 210 and no split products in 692 (Fig. 1). A search of the records revealed *complications in 83 8 % of the* first group of women, in 33 of the second, and in 6.2 % of the third

The complications found in the patients with measurable amounts of split products in the serum are given in Table I Toxaemia (48 cases) and hepatosis (11 cases) were the most common complications. Three patients had glycosuria without known diabetes. Post partum haemorrhage of unknown cause occurred in 3 cases. One patient had severe allergic urticaria and asthma. Another a *multipara, was Rh-negative, and at examination 6* weeks before calculated term she had had a negative antibody test However on that occasion she *had 3 mg/100 ml split products in the serum At* parturition the patient was found to be Rhesus-immunized, and the child required an exchange transfusion.

Three of the infants were jaundiced (serum bilirubin > 15 mg/100 ml) 1 had thrombocytopenia (59 000 platelets mm³) and 3 had anomalies (severe cardiac anomalies, spina bifida and anencephaly). Examination of the mothers had revealed nothing remarkable in these cases. No such anomalies occurred in the infants of mothers without demonstrable split products in the serum.

The frequency of disorders in mothers without split products in the serum was low (Table II).

DISCUSSION

Woodfield et al (15) and Bonnar et al. (1), using modifications of Merskey s hemagglutination inhibition immunoassay (7), found an increase in fibrinolytic split products during the latter part of pregnancy and at parturition. Bonnar et al. (1) also demonstrated high levels of FSP in eclampsia, *abruptio placentae, after intrauterine death* and after postpartum haemorrhage.

Our method does not demonstrate FSP in normal individuals. *We therefore feel that the presence of FSP in serum prepared from blood* samples obtained with addition of an inhibitor of *fibrinolysis argues strongly for the existence of* some disease with a pathological breakdown of fibrin especially since we have found such products in a large series of patients with various diseases, particularly cancer renal disease, acute thrombosis and obstetric complications (5 12).

Among the 1 001 pregnant women in our series

Table I. *Complications found in the pregnant women with fibrinolytic split products in serum*

Diagnosis	No. of cases
Toxaemia	48
Hepatosis	11
Urinary tract infections	9
Glycosuria	3
Postpartum haemorrhage	3
Allergy	1
Rhesus-immunization	1
Severe anomalies of the child	3
Jaundice l the child	3
Thrombocytopenia *in the child*	1
No pathological findings	16
Total	99

Table II *Frequency of complications of pregnancy in women with and without fibrinolytic split products in serum*

	FSP serum		
Diagnosis	Pos 99 cases ( )	Traces 10 cases ( )	Neg 69 cases ( )
Toxaemia	49	20	1 1
Hepatosis	11	3	1 4
Urinary tract infections	9 2	7	1 7
Miscellaneous	14 3	3	0
Total	83 7	33	6.2

> 0.5 mg

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FETAL HEAD GROWTH MEASURED BY ULTRASOUND IN THE LAST FEW WEEKS OF PREGNANCY IN NORMAL, TOXAEMIC AND DIABETIC WOMEN

Pentti Jouppila, Pekka Ylöstalo and Paavo Pystynen

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Abstract. The authors measured the fetal biparietal diameter by an ultrasound technique in 41 normally pregnant women in the 32nd, 36th, 38th and 40th weeks of gestation and found that the diameter increased by an average of 1.8 mm per week. The growth rate decreased as the calculated term approached. In addition, the weekly increase in biparietal diameter was observed in 22 patients in hospital because of toxaemia of late pregnancy and in six pregnant diabetics. Since no significant deviations from normal growth could be shown in these groups of patients, the determination of the fetal biparietal diameter was considered of value for the estimation of the 'true' fetal maturity in toxaemia of late pregnancy and in diabetic pregnancy.

According to earlier reports, the fetal biparietal diameter can be determined in utero by ultrasound and correlates relatively well with the fetal weight (2, 4, 5, 6) and length (3, 5, 6). The reliability of the method was estimated by comparing measurements taken immediately before and after the child's birth. The purpose of the present study was to determine the fetal biparietal diameter by ultrasound in the last few weeks of pregnancy and to observe its weekly growth. Similar studies have previously been reported by Willocks et al. (9), Thompson et al. (8), and Hibbard & Anderson (7).

MATERIAL AND METHODS

The series comprised 41 normal pregnant women, in whom the fetal biparietal diameters were measured by ultrasound in the 32nd, 36th, 38th and 40th weeks of gestation. The women attended the municipal antenatal clinics of Oulu and were examined as outpatients. Owing to delivery prior to term, four patients missed the third examination in the 38th and 19 the fourth examination in the 40th week of gestation. In addition to this normal series, the weekly increase of the biparietal diameter of the fetal head was recorded in patients treated in the Department of Obstetrics and Gynaecology of the University of Oulu. The series consisted of 22 patients with toxaemia of late pregnancy and six diabetics. The measurements in the toxaemic patients were evenly distributed over the 33rd to 41st weeks of pregnancy, while for the diabetic patients all measurements were made before the 38th week. In these pathological groups, the recordings were mostly limited to two or three per patient, depending on the length of their stay in hospital. The ultrasound equipment constructed by Kretz for obstetric and gynaecologic purposes was used (Serie 4000 MG, Kretztechnik, Zipf, Austria). The method of measuring the biparietal diameter was described in an earlier paper (4).

RESULTS

Table I shows the calculated weekly increases in biparietal diameter between the 32nd, 36th, 38th and 40th weeks of gestation. In normal pregnancy the fetal biparietal diameter was found to increase after the 32nd week by an average of 1.8 mm per week. The increase is less rapid as the calculated term approaches.

Figs. 1 and 2 illustrate the growth of the fetal biparietal diameter in normal pregnancy. The curves are based on the mean values of fetal biparietal diameters in the 32nd, 36th, 38th and 40th weeks of pregnancy. Fig. 1 furthermore shows the individual graphs for 22 patients with toxaemia of late pregnancy, indicating in each case the increase in the fetal biparietal diameter during the period when ultrasonic measurements were taken. Since for practical reasons, the consecutive measurements for toxaemic patients could

9 McKay D G. & Goldenberg, V E. Pathogenesis of anatomic changes in experimental toxemia of pregnancy Obstet Gynec 1 651 1963
10. Morris, R. H., Vassalli, P Beller F K. & McCluskey R. T. Immunofluorescent studies of renal biopsies in the diagnosis of toxemia of pregnancy Obstet Gynec 4 32, 1964
11 Nilehn, J -E. Split products of fibrinogen after prolonged interaction with plasmin. Thromb Diath Haemorrh 18 89 1967
1_ Nilsson, I. M Hedner U Isacson, S., Larsson, S. O & Pandolfi, M Symposium on the Side Effects of Coagulation and Fibrinolysis. Milano, 1969 In press.
13 Robbins, J & Stetson, Ch. A. Mechanisms of antigen-antibody reactions upon blood coagulation. Fed Proc 18 594 1959
14 Wardle E. N & Menon, I S. Fibrinolysis in pre eclamptic toxaemia of pregnancy Brit Med J _ 625 1969
15. Woodfield, D G Cole S. K., Allan, A. G E. & Cash, J D Serum fibrin degradation products throughout normal pregnancy Brit Med J 4 665 1968

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Table I *Weekly increase in mm in the fetal biparietal diameter in normal pregnancy*

Week of gestation	No. of patients	Mean (mm/week)	Standard error of the mean	Range
32 36	41	1.9	0.10	2.5
36–38	37	2.0	0.14	3.5
38–40	22	1.3	0.12	2.5
32–40	22	1.8	0.07	1.3

not be effected at the dates corresponding to those of the normal pregnant women the weekly increase in the fetal biparietal diameters of toxaemic patients are not directly comparable with those in normal pregnant subjects. This notwithstanding Fig. 1 reveals that the biparietal diametres in these two groups increased almost in parallel.

Fig. 2 shows the graph for the growth of the fetal biparietal diameter in six diabetic patients. The series is very small Furthermore recordings could not be continued after the 37th week of gestation since the pregnancies of the diabetics were terminated during the 37th week, at the latest. However the graph indicates, that in each case the fetal head grew from the 32nd to the 37th week of pregnancy

DISCUSSION

Earlier reports on biparietal diameters recorded immediately before birth have shown that the error in over 90% of the cases was 0–4 mm, provided the recordings took place during the last trimester of pregnancy (1 4 5 6, 7). In the first two trimesters, the small size of the fetus and the frequent changes in its position make the study of the biparietal diameter too inaccurate and difficult to be of any practical value In the present study observations on the growth of the fetal head started in the 32nd week of gestation In normal pregnancy the mean weekly increase in the biparietal diameter was found to be 1.8 mm, a figure which concurs with the results reported by other authors, viz. 1 6–1 8 mm per week (2, 5 8 9). It was also found that the growth rate decreased as the calculated term approached. This finding is supported by the arrest of the fetal head after the 40th week of gestation previously reported (8).

The growth of the fetal head may of course be slightly slower in toxaemic than in normal pregnancy (9), although this could not be shown in the present series. However any retardation of fetal head growth in toxaemic pregnancy is hardly enough to affect the estimation of maturity Rather it would appear that the fetal head, perhaps, with a few exceptions, grows in toxaemic

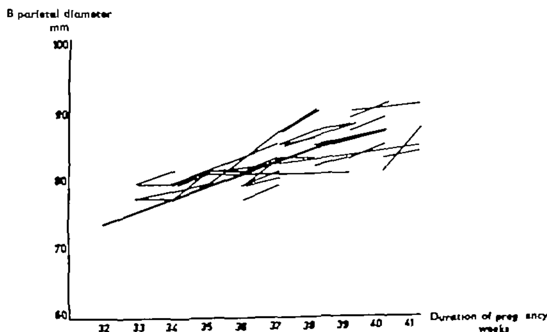


Fig 1 The fetal biparietal diameter in different weeks of gestation in 22 toxaemic patients compared with the mean value curve (heavy line) of the fetal biparietal diameter in normal pregnancy

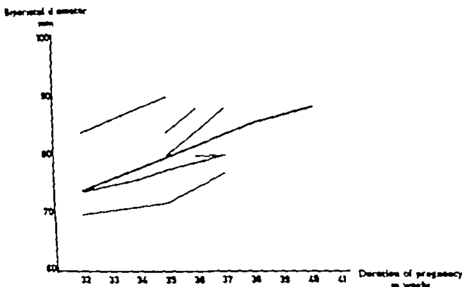


Fig. 2. The fetal biparietal diameter in different weeks of gestation in 6 diabetic patients compared with the mean value curve (heavy line) of the fetal biparietal diameter in normal pregnancy.

pregnancy in the same way as in normal pregnancy. The same appears to be true of diabetic pregnancy. Since it is known that the fetal size in toxaemic pregnancy is often smaller and in diabetic pregnancy larger than the duration of pregnancy would suggest, the true degree of maturity of the fetus in these groups may perhaps be estimated from the biparietal diameter measured by ultrasound.

REFERENCES

1. Anderson, G. V. & Nuwonger, J. W. Cephalometry with ultrasound. Amer J Obstet Gynec 91 563, 1965.
Hibbard, L. T. & Anderson, G. W. Clinical applications of ultrasonic fetal cephalometry. Obstet Gynec 29 842, 1967.
3. Hansmann, M. Die praktische Bedeutung der ultraschalldiagnostik in der Geburtshilfe. Gynaecologia (Basel) 165 127, 1968.
4. Kohorn, E. I. An evaluation of ultrasonic fetal cephalometry. Amer J Obstet Gynec 97 53, 1967.
Kratochwil, A. Die diagnostische Anwendung des Ultraschalles in der Geburtshilfe und Gynäkologie. Zbl Gynaek 88 1032, 1966.
6. Pystynen, P., Ylöstalo, P. & Järvinen, P. A. Foetal cephalometry by ultrasound. Ann Chir Gynaec Fenn 56 114, 1967.
7. Taylor, E. S., Holmes, J. H., Thompson, H. E. & Gottesfeld, K. R. Ultrasound diagnostic techniques in obstetrics and gynecology. Amer J Obstet Gynec 90 655, 1964.
8. Thompson, H. E., Holmes, J. H., Gottesfeld, K. R. & Taylor, E. S. Fetal development as determined by ultrasonic pulse echo techniques. Amer J Obstet Gynec 92 44, 1965.
9. Willocks, J., Donald, I., Duggan, T. C. & Day, N. Foetal cephalometry by ultrasound. J Obstet Gynaec Brit Comm 71 11, 1964.

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THE ALLEGED USEFULNESS OF 6-PHOSPHOGLUCONATE DEHYDROGENASE DETERMINATIONS IN SCREENING FOR UTERINE CANCER

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Abstract. Determination of the enzyme 6-phosphogluconate dehydrogenase in vaginal fluid has previously been suggested as a screening test for uterine cancer. In an attempt to resolve the large discrepancies in the results reported in the literature, some of the factors influencing the stability of the enzyme have been studied. It is demonstrated that the conditions under which the vaginal fluid is handled prior to the assay influence the enzyme activity to a very large extent. Under conditions minimizing denaturation of the enzyme, considerable activity is found in most women. Evidence is presented that in vaginal fluid from women with uterine cancer the enzyme is more stable than in samples from healthy women. The large variations in the results with the conditions under which the samples are handled render measurement of 6-phosphogluconate dehydrogenase in vaginal fluid an unsuitable method for mass screening of uterine cancer.

Considerable efforts have been made to develop biochemical tests which can be used in the screening for cancer. The assay of 6-phosphogluconate dehydrogenase (6-PGD) in vaginal fluid seemed to hold considerable promise as a test for detection of uterine cancer. Thus, many reports have demonstrated that the activity of this enzyme is consistently raised in vaginal fluid from patients with invasive carcinoma of the cervix (2, 4, 6, 7, 10, 11). However, considerable discrepancies exist between the results obtained in carcinoma in situ, and in different studies the percentage of false positive results in women with no malignant lesion has varied from 3% to about 50% (1, 2, 3, 4, 6, 7, 9, 10).

The large discrepancies in these results may be due to several factors. Probably differences in the selection of patients and in the limits set for positive and negative results play a role. However, it appears likely that differences in experimental procedure may be more important. For example, it is possible that differences in the handling of the samples during the time between the collection and the assay may result in different degrees of denaturation. In order to throw some light on this question, a study has been made of some of the factors influencing the stability of the enzyme.

Fellow of the Norwegian Cancer Society

MATERIAL AND METHODS

The clinical material comprises women attending the Out-patient Clinic or admitted to the Gynaecological Department of the Norwegian Radium Hospital. An ordinary gynaecological examination was performed and cytological smears were taken from all patients. The ultimate diagnoses were based on histological examination of biopsies, fractionated curettings, and/or operation specimens. The diagnoses were unknown to the laboratory personnel performing the enzyme assays.

Collection and preparation of samples

Vaginal fluid was collected from the posterior fornix and the external os as previously described (13). The specimens were washed out of the aspirator and transferred to glass tubes with either distilled water, saline, or 0.4 M glycyl-glycine buffer, pH 7.6, containing 10% sucrose. The total volume of the samples and the diluting agent was approximately 1 ml. The samples were either brought immediately to the laboratory or frozen at the temperature of dry ice.

Analytical procedure

The diluted samples were centrifuged at 11 000 rpm for 40 min at 4°C. The supernatant was used for determination of enzyme activity and protein content. The protein content was determined in an Auto-analyzer by the method of Lowry et al. (11).

Table I *Effect of diluting medium on stability of 6-PGD*

Diluting medium	No. of samples	Average decrease in activity (%)	Samples with >90 % decrease (%)
W ter	21	65	33
Saline	14	55	30
Glycyl-glycine buffer (pH 7 6) + 10 % sucrose	37	35	5

The vaginal samples were diluted with different media, as indicated and frozen at −20°C. The activity was measured after storage at this temperature for 10 min and for 24 hours, and the decrease in activity was calculated

The enzyme was assayed spectrophotometrically as previously described (13). *Th. unit of enzyme activity* was defined as the amount of enzyme which could reduce 0.01 μ mole of NADP per minute (2, 13). The specific activity was calculated as the number of enzyme units per gram of protein (13). Samples containing less than 0.3 mg of protein per ml were omitted.

RESULTS

In order to test th stability of 6-PGD under different conditions, experiments were first carried out with a sample of purified 6-PGD from yeast (Boehringer Mannheim, Germany) It was found that the enzyme possessed highest stability when it was diluted and stored in glycyl-glycine buffer containing 10% sucrose, while it was quite unstable when diluted in water The effect of different diluting media on the stability of the enzyme in vaginal fluid was then tested. Specimens were collected from 72 women and washed out of the aspirator with one of the three different diluting media, water saline or glycyl glycine buffer containing sucrose. After thorough mixing each of the specimens was divided into two samples which were frozen quickly at dry ice temperature. One sample was kept for 10 min while the other one was kept for 24 hours at −20 C before the samples were melted and analyzed. The results are shown in Table I It is clear that the stability of th enzyme in vaginal fluid depended strongly on the diluting medium used. When the samples were diluted with water the activity decreased by 65% during storage, and in as much as 1/3 of the samples the activity decreased by more than 90 When diluted with saline the enzyme was only slightly more stable. The highest stability was obtained when the enzyme was stored in the glycyl-glycine buffer containing sucrose. Under these conditions the activity decreased by approximately 35% and only 5% of the samples decreased by more than 90%. Previously we have found (13) that freeze-drying of the samples, a procedure still used by most investigators, caused considerable denaturation of the enzyme an observation which has been confirmed by Gibbs et al. (5).

Since in most previous studies water has been used as diluting medium and also freeze-drying has been employed, *i.e. the samples have been* handled under conditions which render the enzyme unstable, the question arises whether the upper limits for normal values have previously been set *too low and whether this could account for th.* large percentage of false positive tests in some studies. To elucidate this question a study was made of 373 women without malignant disease In this series post-menopausal women and cases of *Trichomonas vaginalis* infection were also ex

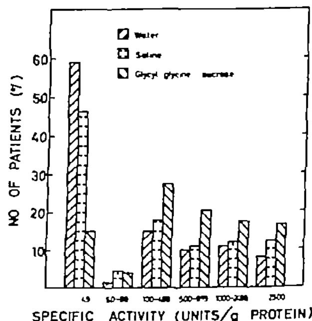


Fig 1 Effect f diluting medium on 6-PGD activity in vaginal fluid from premenopausal omen ithout malignant disease Women with *T ichomonas vaginalis* infection has been excluded. The vaginal fluid as diluted to total volume f about 1 ml ith either ter (110 patients), saline (99 patients) or with glycyl-glycine + 10% sucrose (164 patients). The specimens were then frozen and kept at −20°C for 24 hours before they ere melted and analysed.

cluded as it is well established that the 6-PGD activity is frequently increased in vaginal fluid from such women (2, 3 4 6, 7 10).

The results are shown in Fig. 1 It is clear that, irrespective of the diluting medium used, a considerable fraction of the women had enzyme activities in excess of 50 units per gram protein, the value usually accepted as the upper normal limit. If this criterion was used more than 40% false positive values were obtained in the series where the samples had been diluted with water In the series where saline was used about 57% of the values fell above the upper normal limit whereas in the series diluted with glycyl-glycine buffer as many as 85% false positive values were found. The results clearly show that if the samples are treated in such a way that extensive denaturation is avoided, this will tend to give a higher percentage of false positive results. The data in Fig. 1 further demonstrate that unfortunatel the distribution of enzyme activity in these women is such that no significant improvement in the discrimination between women with uterine cancer and healthy women (or those suffering from benign lesions) can be obtained by setting a higher upper limit for the normal 6-PGD activity

In view of the above results it may seem surprising that in some studies the activity of 6-PGD appeared to be a fairly reliable index of the presence of uterine cancer One possible explanation could be that for some reason the stability of the enzyme is greater in cancer patients than in healthy women Evidence that this is indeed the case is presented in Table II. This table demonstrates that in 16 patients with squamous carcinoma and carcinoma in situ the decrease in the enzyme activity upon storage at $-20°$ for 5 days was far less than in 12 patients with benign lesions. Whereas in the cancer patients the verage decrease in activity was 40% with decrease by more than 90 in 7% of the samples, the average decrease in the patients with benign lesions was 80% and in as many as 40% of the cases the activity decreased by more than 90%

DISCUSSION

The results presented in this study indicate that the large discrepancies reported from different laboratories may to a great extent be caused by the instability of the 6-POD and the consequent loss of enzyme activity after collection of the specimens. It is clear that when the samples are handled under conditions minimizing denaturation of the enzyme, a considerable activity is found in the vaginal fluid from most women. The reason why the activity in many studies has shown a reasonable correlation with the occurrence of uterine cancer seems to be that the stability of the enzyme is greater in samples from cancer patients than in samples from women with benign lesions and from healthy women. One possibility is that the exfoliated cancer cells contain a higher concentration of substances which protect the enzyme during storage. Another possibility is that in uterine cancer isoenzymes with a different inherent stability may be present. Recently Latner & Turner (cf Latner & Skillen (8)) have obtained results which seem consistent with the above views. In studies of the distribution of 6-PGD after starch electrophoresis of extract from cervical carcinomas the bands appeared at different distances from the origin. Addition of excess NADP to the tumour extract was found to abolish the differences in mobility It was pointed out that the results might be due to gene mutation within the tumours. An alternative possibility considered was that cancer tissue may contain more of the coenzyme than normal tissue and that the content of coenzyme may vary in different tumours. It should be noted that the presence of NADP will greatly enhance the stability of the enzyme (unpublished observations).

Whatever the reason for the different stability of 6-PGD in vaginal fluid from cancer patients and from healthy women, the large variations in

Table II. *Stability of 6-PGD activity in different groups of women*[a]

Clinical diagnosis	No. of patients	Average decrease in activity (%)	Samples with >90% decrease (%)
Squamous carcinoma / Carcinoma in situ	16	40	7
Benign lesions	12	80	40

[a] The vaginal samples were diluted in water and frozen at $-20°C$. The activity was measured after storage at this temperature for 10 min and for 5 days and the decrease in activity was calculated.

the results with the conditions under which the samples are handled render measurement of 6-PGD in vaginal fluid an unsuitable method for mass screening of uterine cancer

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REFERENCES

1 Bell, J L. & Egerton, M E. 6-Phosphogluconate dehydrogenase estimation in vaginal fluid in the diagnosis of cervical cancer J Obstet Gynaec Brit Comm 72 603 1965

2 Bonham, D T & Gibbs, D F A new enzyme test for gynaecological cancer Brit Med J 2 823 1962.

3 Boyd, J T Gibbs, D F Labrum, A. H. & Phillips, F R. Cervical screening for carcinoma, comparison of cytological and enzyme (6-phosphogluconate dehydrogenase) methods and clinical findings. Brit Med J 2 785 1967

4 Cameron, C. B. & Husain, O A. N 6-Phosphogluconate dehydrogenase activity in vaginal fluid. limitations as a screening test for genital cancer Brit Med J 1 1529 1965

5 Gibbs, D F Labrum, A. H. & Stagg, B. H. Vaginal fluid enzymology A new assay method with enzyme/potassium ratios. Amer J Obstet Gynec 102 982, 1968

6 Hoffman, R. L. & Merrit, J W 6-Phosphogluconate dehydrogenate in uterine cancer detection. Amer J Obstet Gynec 92 650, 1965

7 Kolstad, P Bergsjø P Koller O., Pihl, A. & Sanner T Detection of preinvasive and early invasive cancer by 6-phosphogluconate dehydrogenase determinations. Amer J Obstet Gynec 98 804 1967

8 Latner A L. & Skillen, A. W Isoenzymes in Biology and Medicine Academic Press, London and New York, 1968

9 Lawson, J G. & Watkins, D K Vaginal fluid enzymes in relation to cervical cancer J Obstet Gynaec Brit Comm 72 1 1965

10. Longnecker D S. & White, C. A. Vaginal fluid 6-phosphogluconic dehydrogenase activity in relation to uterine malignancy Amer J Obstet Gynec 93 1088 1965

11 Lowry O. H Rosenbrough, N. J Farr A. L. & Randall, R. J Protein measurement with the folin phenol reagent. J Biol Chem 193 265 1951

12. Nerdrum, H. J The activity of 6-phospho-gluconic acid dehydrogenase in vaginal secretion. A comparative study of the activity in women with and without gynecological cancer Scand J Clin Lab Invest 16. 656 1964.

13 Sanner T Bergsjø, P Koller O Kolstad, P & Pihl, A. Technical modifications of the 6-phosphogluconate dehydrogenase test of the vaginal fluid. Amer J Obstet Gynec 98 800, 1967

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PHLEBOGRAPHIC STUDIES OF THE LEG VEINS IN THE FIRST HALF OF PREGNANCY AND DURING ORAL CONTRACEPTION

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Abstract. Phlebographic appearances in the legs were studied during the first half of pregnancy in 46 primigravidae and were compared with those in 42 normal nulligravid women. Phlebography was also performed on 34 of the nulligravid women after 6–12 cycles of oral contraceptive therapy. No differences were demonstrated in either study.

Even in early pregnancy a variety of physiological changes take place. It seems likely that these changes are all brought about by the action of a single hormone, probably progesterone. However the evidence is incomplete (10).

The influence of pregnancy on the venous system has been studied by several authors. Frequently varicosis is found before the uterus is large enough to produce mechanical obstruction of venous flow (16). A high level of progesterone causes more than physiological dilatation of veins as well as of the ureters and gastro-intestinal tract (14). Varicose veins in pregnant women are known to regress rapidly if the fetus dies in utero (12).

Changes in the oestrogen-progesterone balance also manifest themselves in various ways in non-pregnant women (14). It is thus to be expected that changes will occur in the venous system during treatment with oral contraceptives.

During the second half of the menstrual cycle, venous distensibility measured by a plethysmographic method, increases by 20–30% corresponding to the increased production of progesterone (13). Increased distensibility of veins in late pregnancy and during the use of oral contraceptives was observed by Goodrich & Wood (7). They also demonstrated a significant decrease in mean linear velocity of blood flow in the lower leg during pregnancy and also during oral contraceptive therapy.

Both pregnant rabbits and non-pregnant rabbits treated with a combination of norethynodrel and mestranol, display changes in the vein wall consisting of an increase of smooth muscle tissue, fragmentation of the reticulum network and attenuation of the elastic tissue (5).

Boatwright & Kaufman (3) gave a combination of norethindrone (2 mg) and mestranol (0.1 mg) to women for 6–12 cycles. Using uterine phlebography they were unable to demonstrate any pelvic congestion. After 4–12 months treatment with norethisterone and ethinylestradiol (Anovlar®) intravenous urography did not show any dilatation of the ureters (6).

Phlebographic studies of the leg veins have not previously been performed either in early pregnancy or during treatment with oral contraceptives. It was thus considered to be of interest to investigate whether venous changes could be demonstrated phlebographically in these conditions (8).

METHODS

Ascending phlebography was performed by the method of Greitz (8). Ethyl-adrianol (Effortil®), 10 mg was given in the morning and 5 mg was given 1 hour before the phlebography in order to avoid hypotension in the erect position. Examination was carried out in the early afternoon (1–2 p.m.). During examination the woman was reclining on the examination table, placed at 65 degrees to the horizontal plane. A vein of the dorsum of the foot was punctured with Olovson butterfly needle and 60 ml Urografin® 60% were rapidly injected manually. Both the lower part of the leg and the thigh were radiographed, ten films in frontal and lateral views being exposed. The film-focus distance was 100 cm. The first film was exposed immediately after the injection and the rest of the exposures were made as rapidly as possible. The films were exposed at 90 kV and the exposure time was 0.04 sec.

Table I. *Age menarche and sexual debute*

Mean values and ranges

	Group A $n=46$ (years)	Group B $n=42$ (years)
Age	19 0 (14–24)	18.8 (16–23)
Menarche	12.8 (11–15)	12.7 (10–17)
Sexual debute	16.4 (13–20)	17.2 (15–22)

The diameters of the anterior tibial veins were measured just proximal to the talo-crural joint, those of the popliteal veins just proximal to the knee joint and those of the femoral veins just distal to the confluence with the long saphenous vein. No correction for enlargement factor was made since it was shown that this differed by only $\pm 3.5\%$ as judged between points corresponding to veins nearest to or farthest away from the film ( ).

Pregnandiol determination. In all pregnant women (group A) a 24 hours specimen of urine (8 a.m.–8 a.m.) was collected for pregnandiol determination. Analysis performed in duplicate by the method of Klopper (11).

Experimental rror was 10 ,. (4).

MATERIAL

Two groups of women were studied. The first (group A) consisted of 46 consecuti primigravidae in the first half of pregnancy who were undergoing legal abortion on psychiatric or sociomedical grounds. The second group (group B) consisted of 4 nulligravidae who visited the clinic for oral contraceptive advice. This group was selected mong women who had menstruated regularly fo t least 2 years prior to the investigation and had no previous hepatic or psychiatric disorders or thromboses.

This analyses were perf rmed t the Hormonal Laboratory f Sabbatsberg Hospital, Karolinska Institutet, Stockholm (Professor Mirjam F rnhjelm).

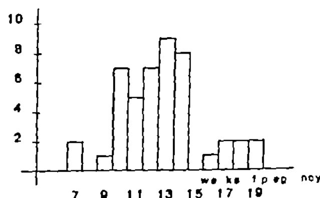


Fig 1. Duration of pregnancy at the time of phlebography (group A).

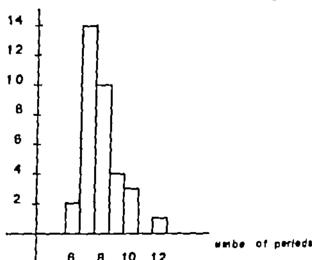


Fig Duration of oral contraception at the time of phlebography (group B).

Ascending phlebography was performed by the technique of Greitz (8), usually on both legs. I group A the examination was performed before abortion and in group B before starting contraception with combination of norgestrel (0.5 mg) and ethinylestradiol (0.05 mg)—Follinyl®— After 6–12 periods of oral contraceptives 34 of the 42 women in group B were reexamined.

A comparison between group A and group B in respect to age, menarche and sexual debute (Table I) show that the groups are comparable.

I group A bilateral phlebography was performed on 43 patients and unilateral examination on 3 patients. The duration of pregnancy t th time of examination is show in Fig. 1 In group B the examination was bilateral in 39 cases and unilateral in 3.

In group B 8 omen were not reexamined by phlebography for various reasons Fo had stopped taking the pills because of illness and mental distress and three had left town. In 1 case puncture f the ein was not successful.

The duration of oral contraception is shown in Fig. 2. The median is 7.5 months.

RESULTS

There was no radiological evidence of thrombosis in any patient in the series Two women in group B already showed varicosis at the time of the first phlebography (before treatment). No varicosis was found in group A

From the data in Table II it is seen that there is no difference between the vein d ameters in the pregnant (A) and the non-pregnant group (B). Nor is any difference found between vein diameters before and after 6–12 cycles of oral con-

e treatment. Although not shown in the difference was demonstrated between the the second half of the menstrual cycle.

pregnandiol content of 24 hours' urine are given in Table III. There is an in- from the first to the second trimester P > 0.01). In two women the collection of led.

Table III. Pregnandiol in mg/24 h in the first and the second trimester

Mean values ± S.E. (standard error of the mean)

Trimester of pregnancy	Pregnandiol (mg/24 h urine) Mean ± S.E.
First	4.2 ± 0.52 (= 21)
Second	5.9 ± 0.53 (n = 23)

DISCUSSION

sts in vascular disorders often report vari- arting in the first trimester of pregnancy arly appearance of primary varicosis is mentioned in obstetric literature. It is also t to ascertain whether or not the observa varicosis represents only an accentuation existing alterations.

nding phlebography was used to examine ns during pregnancy and after a period of ntraception. According to Greitz (8) in nor ses this method seems to give the most in- ion. In measuring the diameters of the there are sometimes difficulties due to a many variants in the normal venous system, s doubled popliteal and femoral veins, vary- currence of valves in the deep veins, wide ion in extent and number of the long and saphenous veins and so on. (For further s see 8, 9 and 17.)

a pilot study both pregnant and non-pregnant n developed hypotonia and even syncope in cases. This resulted in bad venous filling contrast medium, especially in the thigh, and sometimes made the examination impossible. refore in the present series ethyl-adrianol (Ef ®) was given orally on the day of examina-

e II. Measured values of ein diameters

e values and ranges) number of legs examined

	Group A	Group B Before "pills"	Group B After "pills"
erior ed	2.4 mm (2) 88	2.4 mm (2 3) 78	2.2 mm (2 3) 65
liteal n	9.7 mm (7 12) 89	9.7 mm (7 12) 81	9.5 mm (8–12) 65
moral n	10.8 mm (9–13) 89	10.7 mm (9–13) 78	10.9 mm (7 13) 62

tion. This drug possesses a physiological point of action both on the alfa and beta receptor systems. This gives a good balance between the cardiac and peripheral effect of the drug (1), cardiac output rises, the tone in the precapillary sphincters increases but total peripheral resistance decreases (15). — In the present series the same dose of ethyl-adrianol (Effontil®) was given at constant intervals before phlebography. Because of that it does not seem likely that the use of drug has unduly influenced the comparison.

The pregnandiol values found in the pregnant group are almost the same as those found in the normal luteal phase (2–5 mg/24 hours). The relative difference between the first and second trimester presumably depends on the composition of the case material, where the median value is only 12 weeks.

The combination of norgestrel (0.5 mg) and ethinylestradiol (0.05 mg) was chosen as the oral contraceptive because this compound is shown to be very active, inhibiting ovulation in almost 100% (18). In this way we hoped to get a relatively constant level of gestagens in serum during a longer time (6–12 months), avoiding the fluctuations seen during normal menstrual cycle.

By means of ascending phlebography it was not possible to find alterations in distensibility of the leg veins during the first half of pregnancy or during oral contraceptive therapy. Neither was any difference proved to exist between the first and second part of the normal menstrual cycle. This is in agreement with the findings of Sandström (19) who, with a plethysmographic method, found the same distensibility of the leg veins *during the first trimester* of pregnancy and 2 weeks after abortion. However it does not support the findings of Kramer Damrosch & Klink (13) and Goodrich & Wood (7). *In these investigations* plethysmographic methods were used, and the

pregnant group of Goodrich & Wood was in the third trimester when the distensibility might be more pronounced.

REFERENCES

1 Ankerhus, J & Hansen, E. Curr Ther Res *11* 338, 1969
2 Arnoldi, C. C., Greitz, T & Linderholm, H. Acta Chir Scand *132* 507 1966.
3 Boatwright, B. & Kaufman, R. H. Fertil Steril *19* 161 1968.
4. Carlström, K. & Furuhjelm, Mirjam. Personal communication, 1969
5. Danf rth, M., Manalo-Estrella, P & Buckingham, J C. Amer J Obstet Gynec *88* 95., 1964
6. Felding, C. Acta Obstet Gynec Scand *45* 58, 1966.
7 Goodrich, S. M. & Wood, J E. Amer J Obstet Gynec *90* 740, 1964.
8. Greitz, T Acta Radiol (Stockh) *42* 4 1 1954
9 — Acta Radiol (Stockh) *44* 1 1955
10. Hytten, F E. J Obstet Gynaec Brit Comm *75* 1193, 1968.
11 Klopper A., Michie, Eileen A. & Brown, J B. J Endocrin *12* 209 1955
1. Kilbourne, N. J Amer J Obstet Gynec *5* 104 1933
13 Kramer M., Damrosch, L. & Klink, G Handbuch der experimentellen Pharmakologie Band XXII 507 1968.
14 McCausland, A. M. West J Surg *51* 199 1943.
15 Mellander S. Angiologica (Basel) *3* 77 1966.
16. Mullane D. J Amer J Obstet Gynec *63* 620, 195.
17 Nylander G Phlebography *In* Venous and Lymphatic Disorders of the Leg (ed. K. Haeger), chap. X, p. 137 Scandinavian University Books, Lund, 1966.
18 Rice Wray E., Avila, Christina & Gutiérrez, J J Obstet Gynaec *31* 368, 1968
19. Sandström, B. To be published.

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URINARY OESTRIOL EXCRETION IN STRICTLY CONTROLLED DIABETIC PREGNANCIES

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Abstract. Fifty-one strictly controlled pregnancies in 49 insulin-requiring diabetic women were studied. During the last trimester serial analyses of maternal urinary oestriol excretion were performed. A non-intervention programme was adopted, so that the pregnancies were not interrupted before term unless necessary. Serial analyses of maternal oestriol excretion were of great value for the supervision of the pregnancies and for the timing of the delivery provided that the oestriol values were obtained within 6–8 hours after sampling. No intrauterine death occurred and the perinatal mortality was 4%. The urinary oestriol excretion in these diabetic pregnancies corresponded to that in normal pregnancies. No significant differences in excretion were found when pregnancies in women with diabetes belonging to White classes B and C were compared to those with diabetes belonging to class D. Nor was any difference in urinary oestriol excretion found when comparing preeclamptic with non-preeclamptic pregnancies. There was [illegible] significant correlation between infant birth weight at a given gestational age and the maximum maternal urinary oestriol excretion.

The foeto-placental unit produces oestriol which in its conjugated form is excreted in the maternal urine. Several pathological conditions of the foetus and/or the placenta are known to be accompanied by decreased oestriol excretion in the mother's urine. Therefore in such circumstances the condition of the foetus is reflected in the urinary oestriol levels.

Numerous investigations have confirmed the clinical value of repeated determinations of the oestriol excretion in pregnancies complicated by hypertension, preeclampsia, postmaturity, retarded foetal growth and imminent foetal asphyxia (1, 6, 7, 8, 9, 11, 14, 15).

Because diabetic pregnancies are accompanied by a high incidence of complications which could be evaluated by oestriol monitoring, several authors have studied the maternal urinary oestriol excretion in diabetic pregnancies (5, 10, 11, 12, 13, 16, 17, 19, 21, 24). However the variation in results is great, some authors have reported low oestriol excretion while others have found elevated values. These discrepancies can usually be explained by the small number of patients studied, different types of material or varying methods for determination of oestriol. No investigation has included a comprehensive description of the infants.

A prospective study was therefore undertaken on consecutive, rigidly controlled diabetic pregnancies in which serial determinations of urinary oestriol excretion were performed. Fifty-one patients were studied. The size of the series permitted an evaluation of the influence of preeclampsia and the duration of the diabetic disease on the excretion of oestriol. The relationship between infant birth weight and maternal oestriol excretion at different weeks of gestation was also studied. Previous studies on diabetic pregnancies have shown that impending foetal death is accompanied by a progressive drop in oestriol excretion (10, 16, 17, 19, 20, 24). Our goal, contrary to common obstetrical practice, was to avoid premature interruption of pregnancy. Pregnancy was allowed to continue to term or until evidence presented itself that foetal well-being would be jeopardized if the pregnancy continued. Thus the infant complications associated with immaturity were minimized. The condition

Table I *Maternal age prepregnancy weight weight gain during pregnancy and age at onset and duration of diabetes in the whole series*

Mean ± standard error of the mean

	Age (y)	Weight (kg)	Age at onset (y)	Duration (y)	Weight gain d. pregnancy (kg)
Mean	24.0	61.0	12.9	10.9	10.2
S.E.M	0.7	1.3	1 1	0.9	0.5
Range	16–43		1.5–40	1 22.5	

of the foetus was supervised by means of recording of foetal heart rate 4 times daily and by regular determination of oestriol in 24 hours specimens of urine.

MATERIAL AND METHODS

Th diabetic women

The series consisted of 48 women having 51 pregnancies. All had insulin-requiring diabetes. Their ages, weights, weight gains during pregnancy and age of onset and duration of diabetes are given in Table I.

White s (22, 3) classification was used to group the pregnancies (Table II). Class B consisted of patients with an onset of their diabetes after 20 years of ge, a duration of less than 10 years and no clinical evidence of angiopathy Class C included those with an onset between 10–19 years of age a duration of 10–19 years and without angiopathy Class D consisted of patients with an onset before 10 years of age, a duration of more than 20 years or with benign retinopathy Classes F and R included patients with nephropathy and proliferative retinopathy respectively Women with asymptomatic (chemical) diabetes (White s class A) were not included.

The complications during pregnancy were classified according to Pedersen & Pedersen (18). There were seven pregnancies associated with mild preeclampsia (the presence of two or more of the symptoms of blood pressure above 140/90 mgHg, proteinuria above 0.05% or oedema) and one with pyelonephritis. The durations of the pregnancies are given in Table III. Mean gestational times of the total series, of the subgroups according to White classification and of preeclamptic and non-preeclamptic cases are given in Table II.

Table II *Gestational age birth weight and length of the whole series and of the subgroups*

Mean ± standard error of mean

		Gest. age (w)	Birth weight (kg)	Birth length (cm)
Total	Mean	37 4	3.26	49 4
r = 51	S E.M	0.2	0.08	0 4
Whit 's class				
B + C	Mean	37.2	3.36	49.8
= 8 + 4	S.E M.	0.2	0 11	0.4
Whit s class				
D	Mean	37 6	3 29	49 6
= 15	S E.M	0 2	0.16	0.5
White s class				
F + R	Mean	37.0	2.61	46.6
= 3 + 1	S.E.M	0.4	0.28	0.9
M ld preeclamsia	Mean	36.8	3.32	49 4
r = 7	S E.M	0.3	0.19	0.9
Non-preeclamptic	Mean	37.3	3.27	49.5
= 44	S.E.M	0.2	0.11	0.5

Table III. *Distribution of durations of pregnancies*

Gestational weeks	35	36	37	38	39	40
No. of pregnancies	4	8	15	12	11	1

Management

The diabetic women attended special mother's welfare clinic. They were seen every 1 or weeks during the first two trimesters and weekly during the third trimester Samples for morning fasting and afternoon blood glucose estimations were obtained at each clinic visit and urinary glucose output was recorded for the preceding day and night.

When pregnancy was diagnosed, the patients were routinely admitted to hospital for about 1 week. During this period they were examined for signs of retinal angiopathy nephropathy bacteriuria etc. and assigned White classification. An individual diet was prescribed with an intake of 1 600– 000 calories per day (range for series).

The verage percentages of carbohydrate, fat and protein were 45 27 and 8 respectively If the patients previously received insulin once a day two doses per day of insulin of short and middle long acting types were initiated P tients were also instructed bout monitoring their diabetes ith "Clinitest and Ketostix

The women were routinely admitted to hospital on tw further occasions t about the 4th week for 1 week and from the 33rd week of pregnancy until deli ery During these periods blood glucose was determined at least 5 times daily and urinary glucose was monitored on 1 hourly specimens. Further details concerning the degree f diabetic control ill be published elsewhere (Persson & Kellum) Urinary oestriol determinations were performed eekly from the 8th to the 33rd week of gestation and thereafter every 1 or days until deliv ry During the final period in hospital foetal heart rates were recorded four times daily Physical activity was encouraged and the patient took part daily in the physiotherapeutic training programme for expectant mothers.

In 42 pregnancies (84%) caesarean sections were performed; the indications were: retinopathy with suspected progression in 3, failure of induction in 7, persistent fetal bradycardia in 8, consecutive decreases in urinary oestriol excretion in 6, preeclampsia in 5, elective for other reasons in 9 and miscellaneous in 6 pregnancies.

Determination of oestriol in urine

Urinary oestriol excretion was determined using Frandsen (4) method. The standard error of the method in our laboratory was ±11%.

Frandsen demonstrated the specificity of the method using several counter current distribution systems, by Kober spectrophotometry and by comparing values obtained by this method and the specific method of Brown (1). As further test of specificity we checked final extract from pool of pregnancy urine by gas liquid chromatography as acetate on SE-30 and as trimethyl silyl ether on XE-60. In both systems single peak corresponding to the oestriol derivative was the dominating peak on the chromatogram.

Glucose in urine interferes with oestrogen determinations, primarily by destruction of the oestrogens during the acid hydrolysis (2, 12). Using the present method, increasing amounts of glucose added to the urine prior to dilution and hydrolysis did not affect the results (Table IV).

The infants

Mean birth weights and lengths of the whole series, of infants in subgroups according to White and of infants born in preeclamptic and non-preeclamptic pregnancies are given in Table II. There were no significant differences in birth weights and lengths between the groups. Birth weights and lengths of all infants are plotted on the normal intrauterine growth curve given by Engstrom & Sterky (3), Figs. 1–2. Twenty-six per cent of the infants were above the 90th percentile and 14% were below the 10th percentile of the normal weight curves. Sixteen and 12% of the infants were outside the 90th and 10th percentiles of the normal length curve respectively. Apgar scores at 4 min were 9 or 10 in 40 cases, 7 or 8 in 8 cases and 0 in one case. In 2 infants no Apgar scores were recorded.

Among the 51 infants there were two neonatal deaths. A brief description of these 2 cases is given below.

Table IV. *The influence of increasing concentrations of glucose in urine on the analysis of oestriol in 3 different samples*

Glucose % (w/v)	Urinary oestriol mg/l sample no. I	II	III
0	2	6	18.5
2.5	6	2.9	19.2
5.0	3.3	12.9	18.9
10.0	8	3	19.2

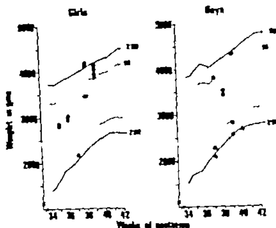


Fig. 1. Birth weights of the whole series plotted against weeks of gestation and sex according to Swedish standards.

N. H. Mother 24 years old, onset of diabetes at 1 year of age, with nephropathy (White class F). During pregnancy mild preeclampsia developed. A boy with a weight of 2.6 kg and a length of 47 cm was delivered by caesarean section at the 36th week. Apgar scores at 1 and 4 min were 10. At 1 hour of age he developed respiratory distress and died at 72 hours. Post mortem examination showed hyaline membrane disease.

G. N. Mother 22 years old, onset of diabetes at 14 years of age, no angiopathy (White class C). A boy with a weight of 2.8 kg and a length of 48 cm was delivered by caesarean section at the 37th week because of irregular foetal heart rate. Apgar scores were 4 at 1 min and 0 at 10 min. He died at 70 min of age. Post mortem examination showed intratentorial haemorrhage.

RESULTS

Urinary oestriol excretion in the whole series

The mean weekly urinary oestriol excretions from the 27th to the 39th week in the 51 diabetic

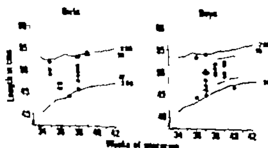


Fig. 2. Birth lengths of the whole series plotted against weeks of gestation and sex according to Swedish standards.

Table V *Weekly urinary oestriol excretion of the whole series and of the subgroups*
Mean ± standard error of mean

Pregnancy week		27	28	29	30	31	32	33	34	35	36	37	38	39
Total material *n* = 51	Mean	8.0	7.8	9.1	9.4	10.3	10.2	12.0	12.7	14.4	16.5	18.8	20.0	23.2
	S.E.M.	0.5	0.5	0.7	0.8	0.6	0.6	0.8	0.7	0.8	0.8	1.1	1.4	2.5
White's class B + C *n* = 32	Mean	8.2	7.9	9.3	9.7	9.7	10.2	12.1	13.5	14.9	16.7	18.4	20.5	24.3
	S.E.M.	0.6	0.6	1.0	1.2	1.2	0.7	1.0	0.8	0.9	0.9	1.2	1.6	1.2
White's class D *n* = 15	Mean	8.0	8.1	9.1	9.1	9.5	11.4	12.6	12.4	14.8	16.5	20.6	21.2	19.8
	S.E.M.	1.1	0.8	1.3	1.3	1.1	1.2	1.5	1.2	1.5	1.6	2.0	2.1	0.4
White's class F + R *n* = 4	Mean						8.4	8.5	7.2	9.7	10.9	14.9	13.9	
	S.E.M.						4.1	3.8	2.1	2.4	4.3	5.9	8.8	
Mild preeclampsia pregnancies *n* = 7	Mean	8.9	8.5	10.5	12.0	11.0	10.7	13.5	14.0	14.8	16.9	22.4	22.3	
	S.E.M.	1.0	0.4	2.1	2.3	2.0	1.3	2.0	1.8	1.8	2.5	3.8	1.6	
Non-preeclamptic pregnancies *n* = 44	Mean	7.6	7.6	8.6	8.5	10.1	10.1	11.4	12.4	14.7	16.7	18.1	19.7	23.2
	S.E.M.	0.6	0.6	0.7	0.8	0.6	0.6	0.9	0.8	0.9	0.8	1.1	1.6	2.5

pregnancies are given in the Table V. The mean values are based upon a total of 675 individual determinations. There was a steady increase from a mean of 8 mg/24 hour at the 27th week to a mean of 23 mg/24 hour at the 39th week. The mean oestriol curve for the diabetic pregnancies, constructed from the means for each patient in each week and the mean of these values to give the points in Fig. 3 was similar to the oestriol excretion curve of normal pregnancies (4).

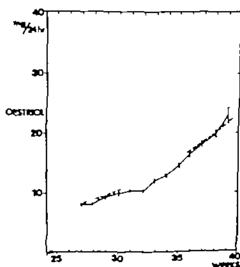


Fig. 3. Mean ± S.E.M. of urinary oestriol excretion in 51 diabetic pregnancies (solid line). The area between the dashed lines includes 95% of the values in normal series given by Frandsen (4).

During the 36th week only 2 patients had values below 9.5 mg/24 hour and during the 38th week only 1 patient had a value that was below 11 mg/24 hour. Both these pregnancies were interrupted before term. In the latter case (N H see above) the infant died in the neonatal period. In 6 patients pregnancy was interrupted mainly because of a decrease of oestriol excretion. In 4 cases this fall was approximately 50% and in 2 cases approximately 30% (Fig. 4). The interruption of the 6 pregnancies occurred in the 36th to the 39th weeks, the infants birth weight varied from 2.8 to 3.6 kg and the Apgar scores at 4 min from 8 to 10. All the infants survived.

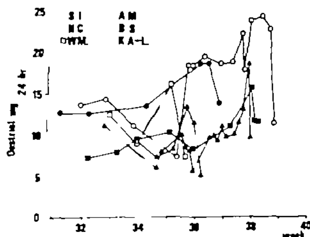


Fig. 4. Individual urinary oestriol excretions in 6 women delivered mainly because of decreasing values.

Urinary oestriol excretion in different White's classes and in women with preeclampsia

When the mean weekly oestriol excretions in diabetic women belonging to White's classes B and C were grouped together and compared to those of women in class D (Table V), no statistical differences between these groups were found during the 27–39th weeks. The mean weekly oestriol excretion in the 4 pregnancies belonging to classes F and R were lower than in the other classes.

When the patients with mild preeclampsia were compared to those without there were no significant differences in urinary oestriol excretions during the 27th–38th weeks (Table V).

Birth weight and urinary oestriol excretion

Irrespective of gestational ages, for the whole series, infant birth weights were significantly ($p < 0.02$) correlated to the maximum mean weekly oestriol excretions. In most pregnancies the maximum mean weekly oestriol excretion occurred in the last week of pregnancy. The regression line was $y = 0.79 + 0.00616\ x$ with $r = 0.60$ when x = birth weight in g.

In order to investigate the relationship between infant birth weight and urinary oestriol excretion at fixed gestational ages, the material was divided into 2 groups consisting of infants with gestational ages between 36–37 and the 38–39 weeks.

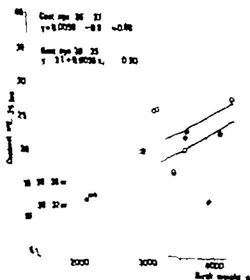


Fig. 5. Correlation between infant birth weight at fixed gestational ages and maternal urinary oestriol excretion.

Table VI. *Maximum oestriol excretion in pregnancies resulting in normal and overweight infants born at the 38th–39th week*

Mean values ± standard error of mean

	No. of infants	Birth weight (kg)	Urinary oestriol excretion mg/24 h
Normal weight	13	3.41 ± 0.10	20.5 ± 1.7
Overweight	8	4.14 ± 0.04	27.0 ± 1.7

The maximum mean weekly oestriol excretion was used as above.

In both groups statistically significant correlations ($p < 0.02$) were found (Fig. 5).

Overweight infants, i.e. above the 90th per centile of the growth curve, born in the 38th and 39th week and infants with normal birth weights of the same gestational age were compared with regard to maximum mean oestriol excretion. The oestriol excretion in pregnancies resulting in overweight infants was significantly higher ($p < 0.02$) than in pregnancies with normal weight infants (Table VI).

DISCUSSION

One of the main complications of diabetic pregnancy is intrauterine death of the foetus. In order to avoid this, in most places the practice has developed to interrupt the pregnancy around the 36th week. This leads to the birth of immature infants with a high neonatal mortality due to diseases of immaturity. To combat the problem of immaturity we have adopted the policy not to intervene during pregnancy unless necessary. This philosophy demands that special attention is paid to maternal and foetal welfare during the last month of pregnancy. Serial analysis of the oestriol excretion in the urine proved to be valuable complement to the following of foetal heart rate and of metabolic control. When oestriol excretion was normal and steadily rising, interruption of pregnancy was not undertaken.

4 of the 51 pregnancies were carried to the 38th week or longer. In spite of this there were no intrauterine deaths. The neonatal mortality was in 51 cases. These infants were born before the 38th week.

Relying upon oestriol excretion, Schwartz et al.

Table V *Weekly urinary oestriol excretion of the whole series and of the subgroups*
Mean ± standard error of mean

Pregnancy week		27	28	29	30	31	32	33	34	35	36	37	38	39
Total material	Mean	8.0	7.8	9.1	9.4	10.3	10.2	12.0	12.7	14.4	16.5	18.8	20.0	23.2
n = 51	S.E.M.	0.5	0.5	0.7	0.8	0.6	0.6	0.8	0.7	0.8	0.8	1.1	1.4	2.5
White's class B+C	Mean	8.2	7.9	9.3	9.7	9.7	10.2	12.1	13.5	14.9	16.7	18.4	20.5	24.3
n = 32	S.E.M.	0.6	0.6	1.0	1.2	1.2	0.7	1.0	0.8	0.9	0.9	1.2	1.6	1.2
White's class D	Mean	8.0	8.1	9.1	9.1	9.5	11.4	12.6	12.4	14.8	16.5	20.6	[illegible]	19.8
n = 15	S.E.M.	1.1	0.8	1.3	1.3	1.1	1.2	1.3	1.2	1.5	1.6	2.0	2.1	0.4
White's class F+R	Mean						8.4	8.5	7.2	9.7	10.9	14.9	13.9	
n = 4	S.E.M.						4.1	3.8	2.1	[illegible]	4.3	5.9	8.8	
Mild preeclampsia pregnancies	Mean	8.9	8.5	10.5	12.0	11.0	10.7	13.5	14.0	14.8	16.9	22.4	22.3	
n = 7	S.E.M.	1.0	0.4	2.1	2.3	[illegible]	1.3	2.0	1.8	1.8	[illegible]	3.8	1.6	
Non-preeclamptic pregnancies	Mean	7.6	7.6	8.6	8.5	10.1	10.1	11.4	[illegible]	14.7	16.7	18.1	19.7	23.1
n = 44	S.E.M.	0.6	0.6	0.7	0.8	0.6	0.6	0.9	0.8	0.9	0.8	1.1	1.6	[illegible]

pregnancies are given in the Table V. The mean values are based upon a total of 675 individual determinations. There was a steady increase from a mean of 8 mg/24 hour at the 27th week to a mean of 23 mg/24 hour at the 39th week. The mean oestriol curve for the diabetic pregnancies, constructed from the means for each patient in each week, and the mean of these values to give the points in Fig. 3 was similar to the oestriol excretion curve of normal pregnancies (4).

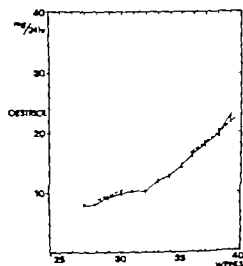


Fig. 3. Mean ± S.E.M. of urinary oestriol excretion in 51 diabetic pregnancies (solid line). The area between the dashed lines includes 95% of the values in a normal series given by Frandsen (4).

During the 36th week only 2 patients had values below 9.5 mg/24 hour and during the 38th week only 1 patient had a value that was below 11 mg/24 hour. Both these pregnancies were interrupted before term. In the latter case (N. H., see above) the infant died in the neonatal period. In 6 patients pregnancy was interrupted mainly because of a decrease of oestriol excretion. In 4 cases this fall was approximately 50% and in 2 cases approximately 30% (Fig. 4). The interruption of the 6 pregnancies occurred in the 36th to the 39th weeks, the infants birth weight varied from 2.8 to 3.6 kg and the Apgar scores at 4 min from 8 to 10. All the infants survived.

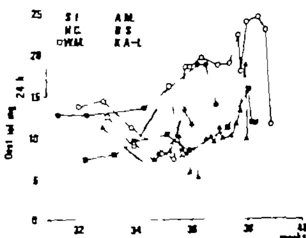


Fig. 4. Individual urinary oestriol excretions . 6 women delivered mainly because of decreasing values.

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MULTIPLE SEVERE MALFORMATIONS IN A CHILD OF A DIABETIC MOTHER TREATED WITH INSULIN AND DIBEIN[1] DURING PREGNANCY

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Abstract. A case of multiple severe malformations in a child of a diabetic mother treated with insulin and dibein (phenformin chloride) during pregnancy is reported. Treatment with oral hypoglycaemic drugs during pregnancy is discussed.

Opinions vary widely as to whether or not oral hypoglycaemic compounds should be used during pregnancy in diabetic women. The safety of such drugs in the treatment of diabetes in pregnancy has been questioned mainly because of the teratogenic effects of large doses of sulphonylureas in rats (DeMeyer 1961, Sterne & Lavieuville, 1964). However there is no evidence that oral antidiabetic drugs are teratogenic in man.

We have recently observed a case where a diabetic mother had been treated with insulin and phenformin (Dibein retard) during pregnancy. The stillborn child showed multiple malformations.

CASE REPORT

B. A., a 22-year-old primigravida, was born on March 3, 1946. Diabetes mellitus was diagnosed in 1960 and she was thereafter treated with insulin. During the 3 years preceding the pregnancy and throughout pregnancy she had insulin treatment in combination with Dibein retard (phenformin chloride) 50 mg twice daily. Her diabetes was under good control and there were no signs of diabetic retinopathy, nephropathy or other vascular complications.

The 33-year-old father of the child is healthy. There is no consanguinity between the parents. Gross malformations or other congenital defects were not known to have occurred among the relatives.

[1] Phenformin chloride (depressed derivate)

The mother's last menstrual period was on 20th April 1968. She was treated with sulphonamide for urinary infection during the 15th week of pregnancy and with penicillin during the 21st week of pregnancy because of an upper respiratory infection. There were no signs of toxaemia, polyhydramnios or other complications during the pregnancy. However she delivered a stillborn child on November 14, 1968, in the 30th week of the pregnancy. The child, a male foetus (Fig. 1) measuring 34 cm in crown-heel length and weighed 900 g. He was moderately macerated and showed multiple severe malformations:

1. Micromelia of the left arm with agenesis of the radius and the metacarpal bones. The left hand was replaced by a single big finger with three phalanges. The top of the finger was covered by a nail. The joints of the interphalangeal bones and the joints of the elbow were normal. The head of the left humerus was irregular but the surface of the left shoulder joint had a normal shape.

2. Moderate micrognathia.

3. Pronounced scoliosis of the spine turning to the left. The left pleural cavity and the left part of the abdominal cavity were markedly narrowed.

4. A huge left-sided abdominal and thoracic hernia comprising part of the heart, the thymus and most of the abdominal viscera (liver, stomach, gut and spleen). The left part of the diaphragm was lacking. The thin sac of the abdominal hernia had ruptured. The attachment of the umbilical cord was situated beside the margin of the hernia. Slight oedema of the face, especially in the periorbital regions, was also seen.

The maceration rendered microscopic examination difficult. Interstitial haemorrhages indicating asphyxia were seen in the lungs. No major pathological findings were disclosed in the microscopic slides from the heart, thymus, kidneys, adrenals or the liver. The pancreas could not be assessed microscopically in a satisfactory way on account of the maceration.

The patient had a further pregnancy and was delivered of a normal healthy child in the spring of 1970. During this pregnancy she was treated with insulin only.

(20) could deliver 16 women out of 20 in a series of diabetic pregnancies in White classes B to F in the 38th week or later They too had no intrauterine death. A "non-intervention program" demands that rigid control of diabetes and active treatment of complications be practiced. Both the absolute level of urinary oestriol excretion and the pattern over a period of time are important factors to consider when timing delivery Low values of urinary oestriol excretion demanded careful consideration as to whether the foetus would be better off in an intra or extra-uterine milieu. At the 36th and 38th week we regard values below 9.5 mg and 11 mg/24 hour respectively to be low These limits are higher than those given by Kyle et al. (16) and Wyss (24), equal those given by Beling (1) and Frandsen (4) but are lower than those of Yousem et al. (25) A fall in urinary oestriol excretion of more than 30–50% during two consecutive days is considered to be a sign of foetal danger Six women in this series were delivered by caesarean section before term mainly because of such a fall in oestriol excretion These infants showed no complications.

When we compared the urinary oestriol excretion in mothers with diabetes of White classes B and C to those in class D no significant difference was found. These results agree with those of Frandsen et al. (5) The duration of the diabetes—and thus possibly the degree of microangiopathy—did not seem to affect the urinary oestriol excretion. However the mothers who had infants classified as overweight for gestational age, did have high oestriol excretions.

Without considering the effects of gestational age, a significant correlation between infant birth weight and maternal urinary oestriol excretion has been recorded in normal pregnancies (1 2) A corresponding correlation was found in this study When birth weights of infants of a fixed gestational age were correlated to the mothers oestriol excretion, a significant agreement could also be found. Thus it appears that infant birth weight at different gestational ages is correlated to the oestriol excretion also in controlled diabetic pregnancies.

REFERENCES

1 Beling, C. G Acta Endocr (Kbh) Suppl. 79 1963
2 Brown, J B Biochem J 60 185 1955
3. Engström, L. & Sterky G. S end. Läkartidn 63 4922, 1966.
4. Frandsen, V The Excretion of Oestriol in Normal Human Pregnancy Munksgaard, Copenhagen, 1963.
5 Frandsen, V Pedersen, J & Stakemann, G. Acta Endocr (Kbh) 40 400 1962.
6. Frandsen, V & Stakemann, G Acta Endocr (Kbh) 44 183 1963
7 Furuhjelm, M Acta Obst Gynec Scand 41 370, 1962
8. Galbraith, R. S., Low J A. & Barton, R. W Amer J Obstet Gynec 106 352, 1970.
9 Greene, J W & Touchstone, J C. Amer J Obstet Gynec 85 1 1963
10. Greene, J W Smith, K., Kyle, G. C., Touchstone, J C. & Duhring, J L. Amer J Obstet Gynec 91 684 1965
11 Heys, R. F Scott, J S Oakey R. E. & Stitch, S. R. Obstet Gynec 33 390, 1969
12 Hobkirk, R., Blakey P R., Alfheim, A., Raeside, J & Joron, C. E. J Clin Endocr 20 805 1960.
13. Joron, G E., Hobkirk, R., Blakey P R., Rautledge, J H. & Fowler A. F Diabetes 11 514 1962.
14 Kellar R., Matthew C. D., MacKay R., Brown, J B. & Roy E. J J Obstet Gynaec Brit Emp 66 804 1959
15 Klopper A. Obstet Gynec Survey 23 813 1968.
16. Kyle, G. C., Yalcin, S., Greene J W & Smith, K. I On the Nature and Treatment of Diabetes (ed. B S. Leibel & G. A. Wrenshall). Exerpta Med, Amsterdam, 1965
17 Pedersen, J The Pregnant Diabetic and Her Newborn. Munksgaard, Copenhagen, 1967
18. Pedersen, J & Pedersen, L M. Acta Endocr (Kbh) 50 70 1965
19 Rhlin, M E., Mestman, J H., Hall, T D Weaver C. P & Anderson, G W Amer J Obstet Gynec 106 875 1970
20. Schwartz, R. H., Fields, G. A. & Kyle, G. C Obstet Gynec 34 787 1969
21 Taylor E. S., Bruns, P D Drose V E. & Kartchner M. J Amer J Obstet Gynec 83 194 1962.
22. White P I Joslin, E. P Root, H. F White, P & Marble A Treatment f Diabetes Mellitus. Lea & Febiger Philadelphia, 1959
23 White P Med Clin N Amer 49 101 1965
24 Wyss, H. J Gynaecologia 167 357 1969
25 Yousem, H. Seitchick, J & Solomon, D Obstet Gynec 5 491 1966

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ported the outcome of 28 diabetic pregnancies treated with diguanides. Twentyfour of the babies were born alive and no congenital malformations were observed. Unfortunately no details are given regarding the gestational age when the therapy was started.

The major malformations shown by the present case have the following incidence at birth according to Rubin (1967): omphalocele 1: 6 000; diaphragmatic hernia 1: 2 200; phocomelia before the introduction of thalidomide 1: 75 000. These malformations usually occur sporadically and no hereditary factors are known. The combination of these malformations is very rare and is not reported to the Swedish register of malformations during the period April 1, 1964 to June 30, 1967. This registration period covered approximately 41 000 births and a total of 2 506 malformed children (Källén & Winberg, 1969). Some of the malformations in our case are similar to those described in the malformed infant whose mother had taken tolbutamide during pregnancy (Larsson & Sterky, 1960), i.e. aplasia of fingers, diaphragmatic hernia.

Concerning the present case it might be argued that it is not justifiable to incriminate a drug for a single example of a multiple malformation. However it is desirable to record all cases of rare malformations seen after treatment of pregnant women with drugs seldom used in pregnancy otherwise it will not be possible to detect teratogenic effects. The diabetic pregnancy is perhaps more susceptible to teratogenic effects than other pregnancies. This may be of advantage for the study of possible teratogenic agents if sufficient patients who have been exposed to suspicious agent are available and if it is possible to compare the findings with those in a control series.

REFERENCES

DeMeyer, R. Teratogenic effects of Sulfonylurea Derivates, 2-Deoxyglucose and Sodium Floro-Acetate in rats. Fourth Congress of the International Diabetes Federation, Geneva, Switzerland, July 10–14, 1961, p. 401.
Glauss, M. H. Chemotherapia 2 342, 1961.
Källén, B. & Winberg, J. Pediatrics 44 10, 1969.
Larsson, Y. & Sterky, G. Lancet 2 424, 1960.
Lenz, W. & Maier, W. Lancet 1 14, 1964.
Milner, J. M., Cooke, A. M., Pyke, D. A. & Fitzgerald, M. G. Brit Med J 2 187, 1964.
Nishimura, H. Chemistry and Prevention of Congenital Anomalies. Ch. C. Thomas Publ., Springfield, 1964.
Passarge, E. & Lenz, W. Pediatrics 37 672, 1966.
Pedersen, J. & Brandstrup, E. Lancet 1 607, 1956.
Pedersen, L. M., Tygstrup, O. & Pedersen, J. Lancet 1 1124, 1964.
Rubin, A. Handbook of Congenital Malformations. Saunders, Philadelphia and London, 1967.
Sterne, J. & Lavieuville, M. Therapie 19 165, 1964.
Stuart, M. D. Pharmindex Jan–Sept. Ag 66.4, 1967.
Torres, H. J. & Victoriano, N. N. Intern J Gyn Obst 7 1, 1969.
Ward, R. Meeting of the European Society for the Study of Drug Toxicity. Medical Tribune, vol. 1, no. 6, 1969.

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Fig 1

COMMENTS

Congenital malformations are noted more frequently among the progeny of diabetic women than in the general population and there is evidence that infants of diabetic women are more often malformed when the diabetes is associated with severe vascular complications (Pedersen 1955 Nishimura, 1964 Pedersen et al., 1964). To date no particular malformation or group of malformations has been identified as characteristic of diabetic embryopathy but there seems to be an overrepresentation of central nervous system, cardiac and skeletal anomalies, especially of the lower extremities and the lower spine (Pedersen et al., 1964 Lenz & Maier 1964 Passarge & Lenz, 1966). However it is not definitely shown what aspect of the metabolic upset is responsible for the teratogenic effect and what kind of treatment might be most beneficial There seems to be no evidence to suggest any teratogenicity of insulin except perhaps in the case of insulin coma (Rubin, 1967). But it is said that the interaction of insulin with other agents such as chloropromazine and salicylates, which act as uncouplers of oxidative phosphorylation may be a factor of importance for teratogenicity (Rubin, 1967). It has also been said recently that diabetes appears to increase the foetal toxicity of thalidomide in rats (Ward, 1969)

The oral hypoglycaemic drug carbutamide given in large doses to pregnant rats induced a number of marked malformations in the foetuses (DeMeyer 1961). Larsson & Sterky (1960) have also reported a malformed infant whose mother had taken the antidiabetic drug tolbutamide during pregnancy The hands and feet of the infant were malformed each hand had only four fingers with syndactyly between the second and third fingers and between the toes. The external ears were malformed and the external auditory canals were atretic. The eyes and optic nerves were normal. There was internal hydrocephalus. The left part of the diaphragm was absent and parts of the stomach, transverse colon, spleen, and pancreas were found in the thoracic cavity There was dextrocardia, complete absence of the atrial septum and a small ventricular septal defect. The right uterine adnexa were absent. Other authors who have given tolbutamide to pregnant women have not had similar unfortunate experiences (Ghanem, 1961 Malins et al 1964) Very little is known concerning the effects of diguanides. Anophtalmia has been observed in the offspring of pregnant rats treated with this drug (Stuart, 1967) Sterne & La Jemville (1964) reported no congenital malformations in the progeny of 15 diabetic women treated with dimethyldiguanide during pregnancy Torres & Victoriano (1969) re

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REFERENCES

DeMeyer R. Teratogenic effects of Sulfonylurea Derivates 2 Deoxyglucose and Sodium Floro-Acetate in rat. Fourth Congress of the International Diabetes Federation, Geneva, Switzerland, July 10–14, 1961 p. 401

Ghosh, M. H. Chemotherapia 2 342, 1961

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Pedersen, L. M., Tygstrup, O. & Pedersen, J. Lancet 1 1124, 1964

Rubin, A. Handbook of Congenital Malformations. Saunders, Philadelphia and London, 1967

Sterne, J. & Lavieuville, M. Therapie 19 165, 1964

Stuart, M. D. Pharmindex Jan–Sept Ag 66. 4, 1967

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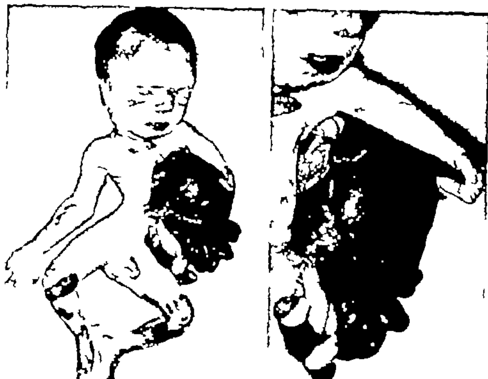


Fig 1

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CANCEROUS AND PRECANCEROUS STATES OF THE CERVIX UTERI

A Histological and Histochemical Study

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Abstract. In the present study one hundred unselected biopsy specimens from the cervix uteri were examined for the presence of 13 chemical substances and 27 specimens for that of 9 enzymes, in an effort to obtain some information on the histochemistry of dysplasia, carcinoma in situ and squamous cell carcinoma of the cervix, on the relationship between precancerous and cancerous lesions of the cervix, and on the usefulness of histochemical studies in clinical practice. A definite correlation was found between the histochemical changes, viz. decrease in the amount of glycogen and increase in the amount of ribonucleic acid and lactate dehydrogenase activity and increasing malignancy. The histochemical changes reflected a disturbance in cell differentiation and keratinization, and stromal reaction. It was concluded that histochemical methods are of value as supplementary tools in differentiating histologically doubtful lesions and in determining later treatment of the patient.

Previous studies have shown that dysplastic changes in the cervix uteri epithelium are associated with an increase in lactate- succinate- and glucose-6-phosphate dehydrogenase activity (13 14, 15 49), in acid phosphatase and nonspecific esterase activity (20 48), and decrease in glycogen (2, 15 24 26, 37 38). Reports on squamous cell carcinoma are contradictory both as regards glycogen (21), and enzymes (7 22), no consistent results have been obtained.

The present study was an attempt to obtain information on the histochemistry of dysplasia, carcinoma in situ and squamous cell carcinoma of the uterine cervix. It aimed also to investigate the relationship between precancerous and cancerous lesions of the cervix, and to devise diagnostic tests based on the histochemical changes, useful for clinical purposes.

MATERIAL AND METHODS

One hundred unselected biopsy specimens from the cervix uteri were examined for the presence of 13 chemical substances and 27 specimens were examined for 9 enzymes. The histochemical properties were correlated to the histological diagnoses by the double blind method. The material was divided into the following groups: normal, dysplasia grade 1 dysplasia grade 2, carcinoma in situ and invasive well differentiated and anaplastic carcinoma. The number and distribution of the lesions is shown in Table I.

Specimens for histological and histochemical studies were preserved in buffered formalin and stained by the following methods: hematoxylin-eosin, Alcian blue-PAS, Masson trichrome, Gomori, methylgreen-pyronine, sulphydryl-disulphide, Gram (8), dihydroxydinaphthyldisulphide stain for SS and -SH groups (1). Specimens were also taken into liquid nitrogen for determination of the following enzymes: alkaline phosphatase (18), acid phosphatase (18), adenosine monophosphatase (47), adenosine triphosphatase (47), aminopeptidase (4), nonspecific esterase (42), succinate dehydrogenase (36), lactate dehydrogenase (25) and glucose-6-phosphate dehydrogenase (25). Oil-Red-O staining for fats was also performed from the frozen-fixed specimens. Control specimens were fixed in Bouin's fluid and the sections stained with Best's mucicarmine stain.

RESULTS

Slight dysplasia, or dysplasia grade 1 was characterized by disturbed stratification of the deeper epithelial layers. Some stratification was seen in the superficial layers. The epithelial cells in the deeper layers were polymorphic, the nuclei were hyperchromatic, and the number of cells had increased. The glycogen normally present in the surface epithelium was reduced, although a PAS-positive zone was locally visible on the surface. The surface layer also showed some Gram-posi-

In Memoriam



Edvard Björkenheim

One of the founders of the Nordisk förening för obstetrik och gynekologi, the Nestor among Finnish physicians and Nordic gynaecologists, Professor Edvard Björkenheim died on February 7 1970 at the advanced age of 93 The cause of death was encephalomalacia.

Asked about his working capacity at the age of 89 when he was promoted to "jubilee doctor" of Helsinki University Björkenheim stated "I haven t been operating for a long time, but at consultations I can still give some advice." Solid workmanship and experience, collected during more than half a century lay behind this remark. The foundation of his education was a B.A in theoretical disciplines, promptly followed by his medical graduation and his qualification for a professorship in 1917 His engagement in one of the two, at this time competing, gynaecological schools of Helsinki probably stimulated him to an enriching efficiency About one hundred publications in his special field, some of which are from the end of the 1950 s, show a lasting interest in science. Appreciation of the medical knowledge and the solid and charming personality of B resulted in honorary memberships and honorary chairmanships in medical societies in and outside of Finland.

B became an honorary member of Finlands gynekologförening 1946 and its honorary chairman 1952, of the Finska läkaresällskapet 1955 the Svenska läkaresällskapet (section of obstetrics and gynaecology) 1954 and of the Société royale belge de gynécologie et d'obstétrique 1929 In 1950 he became the honorary president of the Fédération des sociétées de gynécologie et d'obstétrique de la langue française. He was a corresponding member of the Société d'obstétrique et de gynécologie de Paris since 1927 and of the Deutsche Gesellschaft für Gynäkologie since 1951 The title Professor was bestowed on him 1937

The activities of B as a clinician and an operating gynaecologist were mainly connected with the hospital of Diakonissanstalten in Helsinki. In 1922 he became chairman of the gynaecological department of the same hospital which, thereafter he managed for 33 years. Thanks to his profound training and unusually great knowledge, his skilfulness as a surgeon, organizing capacity and other prominent personal qualities the gynaecological department of Diakonissanstalten developed into a clinic, not only valued by innumerable patients, but also highly esteemed by gynaecologists and other colleagues in his own country as well as abroad. In his clinic numerous young students of medicine made their first tentative efforts in the field of gynaecology

His decease occurred at a time when the epoch of which B was a genuine and exemplary representative seems to be drawing near its end. Regardless of what changes the future will bring, nothing shall ever obscure or mar his memory for those who knew and honoured and ar unreservedly grateful to him.

Harry Zilliacus



Fig. 2. Esterase activity in dysplasia grade 2 of the cervix is increased. Esterase, × 220.

vascular walls. Nonspecific esterase activity was distinct, and aminopeptidase activity weak, in all layers of the surface epithelium, but both were distinct in the stroma. A distinct activity of oxidative enzymes was seen in all layers, except the desquamated surface layer. Lactic acid dehydrogenase activity was strongest. The histochemical properties can be seen from Table II.

In *dysplasia grade 2* the stratification was disturbed in all layers of the epithelium. The cells varied in size and shape, the nuclei were hyperchromatic, and mitoses were also visible in the superficial layers. The basal membrane was intact throughout. The histochemical changes were more pronounced than in dysplasia grade 1. No glycogen was visible in the epithelium, only some acidophil mucosubstances. The surface layers also stained Gram-positively. The ribonucleic acids and SH-groups increased. The histochemical changes in the subepithelial tissues were the same as in dysplasia grade 1.

The changes in enzyme activity were also more pronounced. The stroma was characterized by strong phosphatase activity, distinct nonspecific esterase activity (Fig. 2), and weak aminopeptidase activity. Oxidative enzyme, mainly lactate dehydrogenase, activity was seen in all epithelial layers. The histochemical changes are presented in Table III.

The lesions classified as *carcinoma in situ* colud be divided into two subgroups depending upon the cytologic properties of the epithelium. In the "squamoid" lesions the nuclei were varying in size and shape, and often multilobate nuclei were present in a single cell. The cytoplasm showed an abundance on NH_2-groups

Table III. *Dysplasia grade 2*

Stainability: 0 = none, 1 = slight, 2 = moderate, 3 = strong

	Epithelium	Stroma
Glycogen	0–1	0–1
Acid mucopolysaccharides	0–1	1
Desoxyribonucleic acid	2	1
Ribonucleic acid	3	1
SS groups	1	1
SH groups	0–1	1
–NH groups	2	1
Neutral fats	0	0
Alkaline phosphatase	0	2
Acid phosphatase	0–1	2
Adenosine monophosphatase	0–1	2
Adenosine triphosphatase	0–1	2
Aminopeptidase	0–1	1
Nonspecific esterase	2	1
Succinate dehydrogenase	2	1
Lactate dehydrogenase	2	1
Glucose-6-phosphate dehydrogenase	2	1
Argyrophilic fibres		2
Collagen fibres		1
Elastic fibres		1
Mast cells		1 2
Inflammatory cells		0–2

Table I Distribution of the material

Group	No. of specimens
Normal	15
Dysplasia grade 1	16
Dysplasia grade	15
Carcinoma in situ	18
Well differentiated carcinoma	15
Anaplastic carcinoma	11

Table II. Dysplasia grade I

Stainability 0 = none 1 = slight, – moderate 1 = strong

	Epithelium	Stroma
Glycogen	1	1
Acid mucopolysaccharides	1	1
Desoxyribonucleic acid	1	1
Ribonucleic acid		1
–SS groups	1	1
–SH groups	0–1	1
–NH groups		1
Neutral fats	0	0
Alkaline phosphatase	0	
Acid phosphatase	1	
Adenosine monophosphatase	1	
Adenosine triphosphatase	1	
Aminopeptidase	1	1
Nonspecific esterase	1	1
Succinate dehydrogenase		1
Lactate dehydrogenase		1
Glucose-6-phosphate dehydrogenase		1
Argyrophilic fibres		
Collagen fibres		1
Elastic fibres		1
Mast cells		1
Inflammatory cells		0–

tive matter With the staining method used, the –SS-groups decreased while the –SH-groups increased. *The –NH-groups had increased* and showed uneven staining of the chromatin and chromatin clumps. The squamous epithelium, especially its superficial layers, was characterized by increased pyroninophilia (Fig 1) which indicated an increased quantity of ribonucleic acid, while there was also a slight increase in desoxyribonucleic acid The histochemical changes in the subepithelial tissues were weak. The number of inflammatory cells had increased. Though mast cells were scarce some were seen beneath the dysplastic epithelium Collagen fibres had thickened and were locally fragmented. There was also a subepithelial zone of alcianophil acid mucopolysaccharides.

The distribution of the enzymes examined conformed with the histologic changes. Alkaline phosphatase activity was not found in the dysplastic epithelium, only in the fibroblasts of the subepithelial tissues and in vascular walls. Acid phosphatase activity was seen, though weakly in *the superficial layers*, adenosine monophosphatase and adenosine triphosphatase activity in the surface epithelium, in the stromal fibroblasts and in

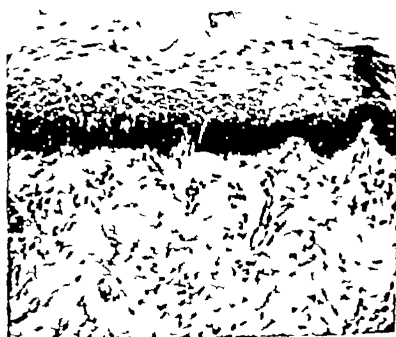


Fig. 1 Dysplasia grade 1 in the cervix showing an increase in the amount of ribonucleic acids in the basal cell layers. Methyl green-pyronine ×220.



Fig. 2. Esterase activity in dysplasia grade 2 of the cervix is increased. Esterase, × 220.

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Table III. *Dysplasia grade 2*

Stainability: 0 = none; 1 = slight; 2 = moderate; 3 = strong

	Epithelium	Stroma
Glycogen	0–1	0–1
Acid mucopolysaccharides	0–1	1
Desoxyribonucleic acid	2	1
Ribonucleic acid	1	1
SS groups	1	1
–SH groups	0–1	1
NH_2 groups	2	1
Neutral fats	0	0
Alkaline phosphatase	0	2
Acid phosphatase	0–1	2
Adenosine monophosphatase	0–1	2
Adenosine triphosphatase	0–1	2
Aminopeptidase	0–1	1
Nonspecific esterase	2	1
Succinate dehydrogenase	2	1
Lactate dehydrogenase	2	1
Glucose-6-phosphate dehydrogenase	2	1
Argyrophilic fibres		2
Collagen fibres		1
Elastic fibres		1
Mast cells		1–2
Inflammatory cells		0–2



Fig 3 Carcinoma in situ of the cer showing some glycogen in the tumour e thelium and a significant amount of a mucopolysaccharides in the stroma. Alc blue-PAS, ×240.

Table IV *Carcinoma in situ*

Stainability: 0 = none, 1 = slight, 2 = moderate, 3 = strong

	Squamoid type		Basaloid type	
	Epithelium	Stroma	Epithelium	Stroma
Glycogen	1	0–1	0	0–1
Acid mucopolysaccharides	1	0–2	0–1	0–2
Desoxyribonucleic acid	1 2	1	1 2	1
Ribonucleic acid	2	1	2 3	1
–SS groups	1 2	1	1 2	1
–SH groups	0–1	0–1	0–1	0–1
NH groups		1	3	1
Neutral fats	0	0	0	0
Alkaline phosphatase	0–1	2	0–1	2
Acid phosphatase	0–1	1	1	1
Adenosine monophosphatase	0–1	2	0	1 2
Adenosine triphosphatase	0–1	2	0	1 2
Aminopeptidase	0	0	0	0
Nonspecific esterase		1	2	1
Succinate dehydrogenase	2	1	2	1
Lactate dehydrogenase	2	1	2 3	1
Glucose-6-phosphate dehydrogenase	2	1	2	1
Argyrophilic fibres		1		1 2
Collagen fibres		0–		0–2
Elastic fibres		1		1
Mast cells		0–2		0–2
Inflammatory cells		0–2		0–2

and sometimes also evidence of glycogen (Fig. 3). The "basaloid" celltype had densely condensed nuclear chromatin and relatively little cytoplasm containing ribonucleic acids and having a strong lactate dehydrogenase activity.

The stromal changes were different in different specimens, and did not correlate to the epithelial cell type. In some specimens a pronounced increase in mononuclear cells and alcianophil mucosubstances as well as a limited amount of mast cells was seen, changes very weak in the stromal tissues of other specimens. The histochemical changes are summarized in Table IV.

Invasive carcinomas could be divided into two subgroups on the basis of their histological and histochemical properties. Subgroup 1 was composed of well differentiated tumours characterized by a pronounced tendency to keratinization, subgroup 2 of anaplastic tumours with poorly differentiated cells and marked cytologic abnormalities.

The cells of the well differentiated tumours showed large quantities of ribonucleic acid and acid mucosubstances. Some cells in the central area of the tumour also showed glycogen. The NH_2 groups had increased, while –SS-groups were few. The keratin cysts showed gram-positively staining keratin. There was a distinct alkaline

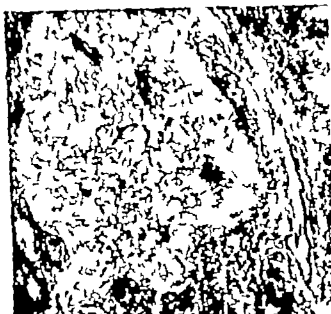


Fig. 4. Tumour islet composed of well differentiated cells showing some adenosine triphosphatase activity in the tumour tissue and strong activity in the surrounding tissues. Adenosine triphosphatase × 220.

phosphatase and adenosine triphosphatase activity around the keratin cysts (Fig. 4). The oxidizing enzymes were regularly distributed in the form of small granules around the nucleus. No activity was visible in the keratin cysts. In the tumour cells, lactate dehydrogenase activity was pronounced. Most of the basal membrane had disappeared, though remnants were visible around some islets.

A distinct *stromal reaction was also visible*. Connective tissue proliferation and inflammatory reaction could be seen around the tumour islets. There was a connective tissue zone containing acid mucopolysaccharides in the intercellular ground substance surrounding the tumour cells. Alkaline phosphatase and adenosine monophosphatase activity was strong in the fibroblasts and vascular walls, but only moderate in the intercellular ground substance. The histochemical changes are presented in Table V.

Subgroup consisted of anaplastic cells growing as cords and small fascicles deep in the surrounding stroma. The phosphatase activity of the tumour cell was weak, although some cell showed marked alkaline phosphatase and adenosine monophosphatase activity. Oxidative enzyme activity was completely disordered and occurred in clumps in the cytoplasm (Fig. 5). Lactate dehydrogenase activity was very irregularly distributed and strong while succinate dehydrogenase activity was weaker than in subgroup 1 tumour cells.

The stromal connective tissue showed *fragmentation* and dissolution of collagen fibres, and degeneration of elastic fibres. Phosphatase ac

Table V. *Invasive carcinoma, well differentiated type*

Stainability: 0 none; 1 slight; 2 moderate; 3 strong

	Epithelium	Stroma
Glycogen	1	0–1
Acid mucopolysaccharides	0–1	0–1
Deoxyribonucleic acid	1	1
Ribonucleic acid	2	1
SS groups	1	0–1
SH groups	0	0–1
NH_2 groups	2	1
Neutral fats	0	0
Alkaline phosphatase	0	2
Acid phosphatase	1	2
Adenosine monophosphatase	0	2
Adenosine triphosphatase	1	2
Aminopeptidase	0	0
Nonspecific esterase	2	1
Succinate dehydrogenase	2	1
Lactate dehydrogenase	2	1
Glucose-6-phosphate dehydrogenase	2	1
Argyrophilic fibres		2
Collagen fibres		2
Elastic fibres		1
Mast cells		0–1
Inflammatory cells		0–2



Fig 5 Anaplastic squamous cell carcino[illegible] of the cervix showing a strong and [illegible] regularly distributed lactate dehydrogena[illegible] activity Lactate dehydrogenase, × 45

Table VI. *Invasive carcinoma anaplastic type*

Stainability 0 = none 1 = slight [illegible] = moderate 3 = strong

	Epithelium	Stroma
Glycogen	0	0
Acid mucopolysaccharides	0	0–1
Desoxyribonucleic acid	1	1
Ribonucleic acid	3	1
–SS groups	1	1
–SH groups	0	0
NH groups	3	1
Neutral fats	0	0
Alkaline phosphatase	0	1
Acid phosphatase	0	1
Adenosine monophosphatase	0	1
Adenosine triphosphatase	0	1
Aminopeptidase	0	0
Nonspecific esterase	2	1
Succinate dehydrogenase		1
Lactate dehydrogenase	3	1
Glucose-6-phosphate dehydrogenase		1
Argyrophilic fibres		1
Collagen fibres		1
Elastic fibres		1
Mast cell		0
Inflammatory cells		0–3

tivity in the stroma was weak, and aminopeptida[illegible] activity absent. The histochemical changes are r[illegible] viewed in Table VI.

These studies showed that the histochemic[illegible] properties of the human cervix uteri conform[illegible] well to the histopathologically visible changes se[illegible] in the cervix. The most reliable indicators of i[illegible]cipient malignancy were the decrease in glycoge[illegible] (Fig. 6), and increase in ribonucleic acids (Fig. 7[illegible]) and lactate dehydrogenase activity (Fig. 8).

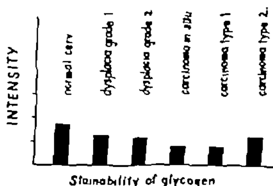


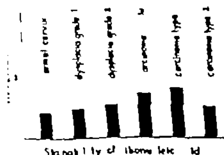
Fig 6 Visual evaluation of the intensity of glycogen staining.

DISCUSSION

sults of the present histochemical studies a definite correlation between the histo-ally and histologically detectable changes. crease in glycogen was one of the most indicators of increasing malignancy. Ear dies have revealed a disappearance of gly through all grades of anaplasia (24). This the basis underlying the so-called Schiller he presence of glycogen in carcinoma has uestioned (15 19). The explanation might t there are two types of squamous cell car a, a differentiated type with intracellular gen, and an anaplastic type devoid of gly-. The increase in ribonucleic acid was also cant, showing a greater increase in anaplastic in ell differentiated carcinomas.

other indicator of malignancy was the in- in epithelial oxidative enzyme activity. The tive enzyme activity of dysplastic epithelial was significantly increased in the dysplastic elium, showing the increased metabolic ac and increased ratio of anaerobic glycolysis e cells. A noticeable finding was also the ir lar distribution of oxidative enzymes in ana ic carcinomas, compared to the regular dis tion in well differentiated carcinomas.

stochemical studies also showed definite re ship between the dysplastic states and in- ve carcinomas. The evidence acquired in the ent study suggests gradient of increasing ignancy from dysplasia grade 1 and dysplasia de to carcinoma in situ and invasive car oma. The histochemical changes reflect a dis- ance in the normal differentiation of cells n basal to parabasal and superficial cells, and



g. 7. Visual evaluation of the intensity of ribonucleic id staining



Fig. 8. Visual evaluation of the intensity of lactate dehydrogenase activity

by the production of abnormal cell forms showing a tendency to pathological keratinization (2, 44).

The significance of the two cell forms constituting carcinoma in situ could not be ascertained in the present study. The "squamoid" type, only little different from carcinoma in situ was similar to the spinal cell carcinoma of Matzloff (34), differentiated carcinoma of Reagan & Hicks (43), type III carcinoma of Fluhman (12) and α carcinoma of Olds et al. (40). The more immature "basaloid" cell type was similar to the celltype seen in transitional cell carcinoma of Matzloff (34), small cell carcinoma of Friedell et al. (16), undifferentiated carcinoma of Reagan & Hicks (43) type I carcinoma (12) or γ carcinoma (40). Histochemically these celltypes also showed differences in the amount of mucosubstances, glycogen, ribonucleic acids and oxidative enzyme activity.

The role host resistance in the manifestation of cervical epithelial neoplasia has been almost completely overlooked. In connection with studies on pulmonary neoplasms Korhonen & Mäkelä (30) assumed that acid mucosubstances were associated with immunological processes in the organism. The stromal mucosubstances have been considered to be a local defence reaction of the organism (3 31 33). Many investigators have supported the iew that mast cells inhibit the growth of the neoplasm (11 41) by activating the defence mechanisms of the organism (50). Japanese investigators (27 28) found that when a strong round cell reaction was seen patients suffering from carcinoma had better prognosis. Csaba et al. (6) considered the round cell reaction to be an expression on the cellular level of immunological

reactions of the entire organism, mediated primarily by lymphocytes (29) The host defence reaction might be an explanation why cancer in situ with very immature and actively diving cells, is a relatively slowgrowing lesion and in some cases *might* even regress spontaneously The stromal reaction may perhaps have clinical significance in determining the fate of these lesions, as the stromal reaction in progressing and regressing skin tumours is different (45). The stromal reaction whether it is a proliferative or destructive one (23) has been shown to correlate to the growth pattern of skin tumours (46) so the stromal changes seen in this study may have prognostical significance.

Enzymatical studies have also been performed in an effort to evaluate the stromal reaction. The aminopeptidase activity has been taken as an indicator of this (35), although some authors consider the aminopeptidase activity to indicate the invasive property of the neoplasm (5). In this study the aminopeptidase activity was visible around the dysplastic epithelium and carcinoma in situ but absent around invasive anaplastic carcinomas.

To distinguish between malignant, premalignant and inflammatory cells and tissues purely histochemically was difficult for several reasons. An accurate estimation of the histochemical reaction enzyme activity and amount of end product was hard to achieve by purely visual means. A cell containing no final reaction product can be distinguished from one containing much, but the eye cannot detect the difference between cells containing an "average amount and other containing slightly more or less than the average Even if small variations in the concentrations of the final reaction products were visible, it would be very difficult to obtain strictly comparable results by the histochemical methods currently in use. To express the results in an understable manner and still adequately and accurately is a matter which also has not been settled. Time interval and temperature difference between taking the specimen and its treatment affects the final result and so does the pH, ionic strength, period of staining etc. The acridine-orange method has been widely used (3_) in histochemical studies but proved not to b reliable enough for routine use. However histochemical methods can be used as a multiparameter approach to the problem of differentiating neoplastic states in the cervix. Histochemical studies using several stains and determination several enzymes, may be a supplementary tool histological studies.

REFERENCES

1 Barrnett, R. J & Seligman, A. M. J Nat Cancer I 14 769 1954
2 Bejdl, J W Z Zellforsch 40 389 1954
3 Bottiglioni, E. & Prodi, G Sperimentale 107 1 1961
4 Burstone, M. S. & Folk, E. J Histochem Cytoch 4 217 1965
5 Carr et al. Brit J Cancer 2 714, 1968.
6 Csaba et al. Brit J Cancer 15 377 1961
7 Dawson, I. M P & Filipe, M L. J Obst Gyn Brit Comm 74 43_, 1967
8 Ernst, P Arch Mikrosk Anat Entwicklungsg 47 66 1896.
9 Farber E. J Histochem Cytochem 4 284 1956.
10. Filipe, M I & Dawson, I. M. P J Path Bact 9 243 1968.
11 Fisher E. R. & Fisher B Arch Path (Chicago) 7 185 1965
12. Fluhman, C. F The C rvix Uteri and its Disease Saunders, Philadelphia, 1961
13. Foraker A. G. & Denham, S. W Tex Rep Bi Med 11 643 1953
14 — Amer J Obst Gyn 74 131 1957
15 Foraker A. G & Marino G Amer J Obst Gyn 7 400, 1956.
16. Friedell, G H, Hertig, A. T & Younge P A. Carcinoma in situ of the uterine cervix—A study of _3 cases from the Free Hospital for Women. C. Thomas Springfield, Ill., 1960
17 Fuhrmann, K. Zbl Gynaek 83 213 1961
18. Gomori, G Microscopic Histochemistry Theory and Practice. The University f Chicago Press, Chicago Ill 195_
19 Gothie, S. Rev Franc Gyn Obstet 56 631 1961
20. Gross, S. & Danziger S Amer J Obst Gyn 73 94 1957
21 Gross, S. & Kinzie G Obst & Gyn 15 261 1960.
22 — Obst & Gyn 19 _8 1962.
23 Hamperl, H. Virchows Arch Path Anat 340 185 1966.
24 Henry J S. & Latour J P A Amer J Obst Gyn 74 610, 1957
25 Hess et al. J Biophy Biochem Cytol 4 753, 1957
26. H pman, B. C Amer J Obst Gyn 79 346, 1960
27 Inokuchi et al. Cancer (Philadelphia) 20 19 4 1967
28. Kawamata t al Geka Shinry 7 285 1962
29 Klein, G An Rev Microbiol 20 223 1966
30. Korhonen, L. K & Makela, V Histochem J 1 1 4 1969
31 Lengyel, J & Szemeal, I Gynaecologia (Basel) 140 116, 1955
3_ Louis, C. J Obst & Gyn 72 336, 1960.
33 Maltoni, C. Nature 18 174_, 1958
34 Matzloff, H. K. Bull Johns Hopkins Hosp 34 141 19_3

35 Mottet, N. K. Amer J Path 39 17 1961
36 Nachlas et al Histochem Cytochem 5 420, 1957
37 Nogales-Ortiz, F & Botella-Llusia, J Arch Gynaek 197 450, 1959
38 — Arch Gynaek 192 644, 1960.
39 Novak, R. E. & Woodruff, J D Gynecologic and Obstetric Pathology 6th ed. Saunders, Philadelphia, 1967
40 Old et al Cancer (Philadelphia) 18 1598 1965
41. Orlandi, G Ann Laring 60 325 1961
42. Pearse, A. G. E. Histochemistry Theoretical and Applied, 2nd ed J & A. Churchill, London, 1961
43 Reagan, J W & Hicks, O. J Cancer (Philadelphia) 6 1200, 1953.
44 Steiner K Arch Derm 79 436, 1959
45 Stenbäck, F Ann Med Exp Fenn 47 92, 1969 a.
46. — Acta Path Microbiol Scand, Suppl. 208 1 1969 b
47 Wachstein, M. & Meisel, E. Amer J Clin Path 27 13, 1957
48. Waronski, W Zbl Gynaek 88 66, 1966.
49 Wady K. & Kierski, J Acta Cytol (Philadelphia) 11 431 1957
50. Zechner G Mschr Ohrenheilk 99 420, 1965

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REFERENCES

1 Barrnett, R. J & Seligman, A. M., J Nat Cancer Inst 14 769 1954
2 Bejdl, J W Z Zellforsch 40 389 1954.
3 Bottiglioni, E. & Prodi, G., Sperimentale 107 150, 1961
4 Burstone M S. & Foll., E., J Histochem Cytochem 4 17 1965
5 Carr et al., Brit J Cancer 2 714 1968.
6. Csaba et al., Brit J Cancer 15 377 1961
7 Dawson, L M P & Filipe, M. L. J Obst Gynaec Brit Comm 74 43., 1967
8. Ernst, P Arch Mikrosk Anat Entwicklungs 47 669 1896.
9 Farber E., J Histochem Cytochem 4 284 1956.
10 Filipe M. I & Dawson, I. M. P J Path Bact 9 243 1968.
11 Fisher E. R. & Fisher B Arch Path (Chicago) 7 185 1965
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13 Foraker A. G & Denham, S. W Tex Rep Bi Med 11 643 1953
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15 Foraker A. G. & Marino G. Amer J Obst Gyn 7: 400, 1956.
16. Friedell, G. H., Hertig, A. T & Younge, P A Car cinoma in situ of the uterine cervix—A study of .3 cases from th. Free Hospital for Women. C. Thomas Springfield, Ill., 1960.
17 Fuhrmann, K. Zbl Gynaek 83 213 1961
18 Gomori, G Microscopic Histochemistry Theory an Practice The University of Chicago Press, Chicago Ill., 1952.
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22. — Obst & Gyn 19 28, 196_
.3 Hamperl, H Virchows Arch Path Anat 340 185 1966.
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33 Maltoni, C Nature 182 174., 1958.
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35. Mottet, N. K., Amer J Path 79 17 1961
36. Nachlas et al Histochem Cytochem *5* 420 1957
37. Nogales-Ortiz, F & Botella-Llusia, J Arch Gynaek *192* 450, 1959
38. — Arch Gynaek *192* 644, 1960.
39. Novak, R. E. & Woodruff, J D Gynaecologic and Obstetric Pathology 6th ed. Saunders, Philadelphia, 1967
40. Old et al Cancer (Philadelphia) *18* 1598 1965
41. Orlandi, G Ann Laryng 60, 325 1961
42. Pearse, A. G. E.: Histochemistry Theoretical and Applied, 2nd ed. J & A Churchill, London, 1961
43. Reagan, J. W & Hicks, O. J Cancer (Philadelphia) 6 1200, 1953
44. Stewart, K., Arch Derm 79 436, 1959
45. Stenbäck, F Ann Med Exp Fenn 47 92, 1969
46. — Acta Path Microbiol Scand, Suppl. 208 1 1969 b
47. Wachstein, M. & Meisel, E., Amer J Clin Path 27 13, 195
48. Waronski, W Zbl Gynaek *88* 66, 1966.
49. Widy K. & Klenski, J Acta Cytol (Philadelphia) *11* 231 1957
50. Zeeboer G., Mschr Ohrenheilk 99 420, 1965

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In Memoriam

Professor Anton C. Sunde was born in Oslo on November 21 1882 and died on December 24 1969 He graduated in medicine from Oslo University in 1909 Afterwards he served as a clinical intern in several departments and institutes at the State Hospital (Rikshospitalet) and Oslo City Hospitals. After studying obstetrics and gynaecology in Copenhagen in 1913 he was appointed to a clinical internship at the old Maternity in Oslo During the years 1914–16 he served as a clinical intern at the new Maternity of the State Hospital and next year at the Dept of Surgery of the same hospital. From 1918–22 he was first assistant at the Maternity of the State Hospital

Having completed his hospital service, he became a private practitioner in his specialty until he was appointed professor and head of the department of obstetrics and gynaecology In this capacity he was in charge of the education of the medical students until his retirement at the end of 1952. Thereafter he was a private practitioner appointed to a private hospital.

Dr Sunde was the first chairman of the Oslo Gynecological Society and a member of the Norwegian Society of Sciences from 1942. He was an honorary member of the Danish Society of Gynecology and Obstetrics, likewise of the similar societies in Sweden and Finland

In 1921 Dr Sunde took his doctor's degree on his thesis Chorioepithelioma malignum. Before and during his time as a professor he was an active contributor in his field, partly by delivering studies to the medical press, partly by making valuable contributions to discussions of the gynaecological societies of Scandinavia He will be remembered as a remarkable personality who greatly influenced Norwegian medicine.

Finn Bøe

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